Introduction and Overview of Cancer Therapeutics

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1.1 Introduction

Cancer has been a significant cause of mortality and morbidity both in developing and developed nations worldwide. Early identification of cancer with reliable diagnostic accuracy has still been one of the mainstay challenges of an oncologist clinic. Moreover, the routine laboratory work carried out for assessing cancer progression is equally discomforting for the patient as the disease itself. Cancer is a multifactorial disorder involving complex modifications in the genome affected by the interactions between host and the environment [16]. The major hallmarks include alteration in cell division patterns, uncontrolled replication, apoptosis evasion, sustained angiogenesis, and metastasis [23].

In the past century, cancer was effectively treated with surgery, chemotherapy, and radiotherapy in combination or either alone and thus produces cures and significant impact on tumor growth. But, once it metastasize, the treatment modalities become more complicated. With the passage of time, it was also perceived that individual treatments of surgery, chemotherapy, or radiation were not very effective [41]. The idea of combined therapy was initiated in 1960's with tremendous improvements in patients' health outcomes and cancer control. Although, the required level of expected outcome in terms of patients survival has not been achieved till date. Characteristics of different tumors are continuously under study, yet some pathways and characteristics are determined to create new revolution in understanding cancers and targeting drugs to tumors [16]. Nowadays, immune mediated therapies, hormonal therapies, biological molecules, gene therapy, and oncolytic viro-therapy. Nanoparticles-based therapies are being used to

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some extent. Although the expected therapy level has not been reached to fight cancer by decreasing the mortality rate and increasing the survival time for the cancers.

1.2 Tumor Biology and Cancer Development

When the body cells fall for uncontrolled growth and do not respond to the normal cell signaling cycle, they proliferate and undergo an abnormal condition known as cancer. If this uncontrolled behavior continues, then the cells spread to the other organs which is called as metastasis, a very fatal condition leading to majority of cancer deaths [23].

During mitosis, the normal cells grow relying to different growth factors and exhibit contact inhibition ability that is after reaching a specific threshold the cell stops dividing, but the cancerous cell grow independently of any such growth factors or signals and also lack contact inhibition ability, leading to the formation of unwanted cells [35]. Other than this, normal cells died by apoptosis and replaced by new cells with limited efficacy of DNA replication, whereas cancer cells show high activity of telomerase enzyme that keep replacing worn out ends of telomere allowing uncontrolled cell proliferation [41].

The cancer develops a large mess of cells known as hyperplasia that is formed due to uncontrolled cellular growth. The next step is dysplasia that is the cell growth accompanied with abnormalities followed by anaplasia in which these atypical cells spreads to the limited area of the tissue [15]. Till this stage the tumor is noninvasive and considered as benign. Later at the advanced stages, the tumor cells metastasize and started invading to the neighboring tissues and organs. Tumor cells require oxygen and nutrient for their growth and proliferation like other normal cells, so they develop their own blood vessels in a process called as angiogenesis. If identified earlier, the cancer can be treated [10].

1.3 Types of Cancer and Grades

Usually, they are named by the type of cells they originate.

Carcinomas originated from epithelial cells and constitute the highest ratio among all cancer types. Sarcomas are formed in bones, muscles, and connective tissues. Leukemias are specific to white blood cells. Lymphoma is the cancer of lymphatic system or cells derived from bone marrow [52]. Myelomas are specific to antibodies synthesizing white blood cells.

Cancer grades represent the abnormality in the cells. Grades are increased from 1 to 4 with the increase in the abnormality in the cells. Well differentiated cells belong to low grade tumors. Poorly differentiated cells are highly abnormal and so are included in high grade tumors [2]. To further elaborate the cells, the following are the criteria for grading:

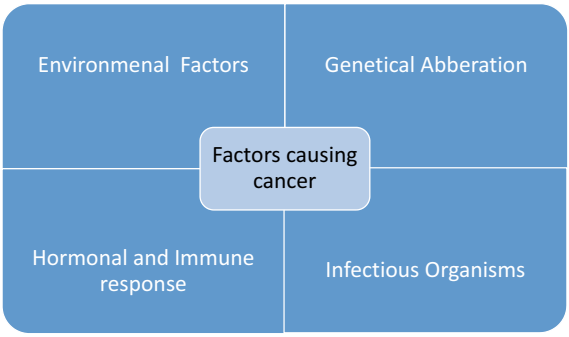

Fig. 1.1 Causative factors for cancer

Grade 1: Well differentiated cells with minor abnormalities.

Grade 2: Bit higher level of abnormality and moderately differentiated cells.

Grade 3: Improperly differentiated cells with highly mutated chromosomes effecting nearby cells and producing harmful chemicals.

Grade 4: Undifferentiated, immature, and primitive cells.

1.4 Factors Involved and Cancer Causes

The initiation and cancer advancement in the body depends on factors like immune conditions, environmental factors, life style, mutations, hormonal imbalance, infectious organism, exposure to radiations and chemicals [23]. Any of these factors may cause abnormal cell growth and uncontrolled proliferation which ultimately lead to tumor and then the spread of these cells to other tissues and organs causing metastasis. Mutations may be in the master genes or tumor suppressor gene that leads to cancer [7]. Abnormal chromosomes replication resulting in the deletion or duplication of entire or partial set of chromosome, defective DNA repair are also considered as one of the cause of cancer spread. Genetic aberration leads to abnormal protein synthesis or modification that may halt the normal protein functioning and thus leading to cancer [44]. At times these changes take months to years to be detectable, also there are several mechanism that involves in cancer development, these factors thus creating it difficult to get cancer diagnosed at earlier stages (Fig. 1.1). However, it is not entirely impossible to detect the cancer at earlier stage.

1.5 Cancer Therapeutic Modalities

Knowing the severity of cancer, extensive research is required to understand the disease diagnosis and therapeutics completely. All the treatment methods which are used to treat cancers still require continuous research to better cope with the

heterogeneity of disease [12]. Along with the basic or bench side research, quality treatment trials are also required. Currently, more than 60% of all ongoing medical treatment trials are concentrating on cancers [12]. Commonly used treatments are surgery, chemotherapy, and radiotherapy which are decided on the type, stage, and locality of cancers [6]. Some of the modern treatment modalities includes hormonal and immunotherapy, antiangiogenic modalities and stem cell therapies, genomic therapy, and oncolytic viro-therapy [15]. Along with these the genetic control, nutritional assessments for cancer patients and psychological treatments all add to the success of the treatment strategy for cancer patients [7, 10]. Further, in this book almost all treatment strategies will be discussed that are helpful in cancer treatment.

1.6 Surgeries

One of the most commonly used modalities is surgery for many benign and malignant tumors. It also has lesser side effects on other associated or neighboring tissues as compared to chemotherapy and radiotherapy. Surgeries can be less invasive or open depending upon localization of tumor, size of tumor removed, patient immune condition, and reason for surgery [50].

During the surgery, entire tumor can be removed or certain specific part can also be removed. Tumor mass can also be debulk and ease the tumor pressure and pain on the certain area. Surgery also improves the chances of successful chemotherapy [9, 24].

During open surgery, a cut is made to remove the tumor mass along with some healthy tissues and lymph nodes to ensure complete removal of tumor mass. While in invasive surgery, a small incision is made, and a thin tube with camera is inserted in the body to see the tumor in detail. With the help of images from the camera, the surgeon decided about the removal of tumor mass using specialized surgical tools [50].

1.7 Chemotherapy

The cancer treatment with chemotherapy dates back to 1930s and was introduced by Paul Ehrlich, a German scientist, while working with alkylating agents. During the World War I and II, the soldiers, exposed to mustard gas, experienced decreased level of leukocytes count which was treated by Gilman in 1943 by nitrogen mustard as a first chemotherapeutic agent to treat lymphomas [1]. These were highly electrophilic in nature and can react with cellular nucleophiles, adding alkyl groups to DNA bases, resulting in cancer cell death. At the same time, another class of antibiotics called antimetabolites (e.g., aminopterin and amethopterin) that interfere with folate synthesis or mimic DNA precursors, halting DNA replication leading to death of cancer cells [20]. After 1948 these antimetabolites were used to treat leukemia in children. Later, cyclophosphamide and chlorambucil were

synthesized to treat cancers. In 1951, 6-thioquanine and 6-mercaptopurine were developed by Elion and Hitchings for treating leukemia [18]. Similarly, a new drug was developed by Heidelberger for solid tumors, 5-fluorouracil (5-FU), which is used as chemotherapy agent against colorectal, head, and neck cancer until now [13]. Prior to chemotherapy, the surgical removal was the only choice to treat tumors.

The national service center for cancer chemotherapy was established in 1955 for testing cancer drugs [42]. At that time monotherapy with corticosteroids was the choice to treat cancers, and the first cancer cured was choriocarcinoma in 1958 [34]. By 1960s, new trends of chemotherapeutic agents with alkaloids from vinca and ibenzmethyzin (procarbazine) were applied to leukemia and Hodgkin's disease [30].

The principal of chemotherapy is controlling tumor progression by halting the cell division and enforcing apoptosis majorly by genotoxic effect that is by production of reactive oxygen species [5]. Tumor cells continuously grow without apoptosis and with very high ratio of cell proliferation and cell death, however, it also effects the normal cells and has some side effects on the body. Out of total chemotherapeutics currently use, only 132 are approved by FDA. These cells also damage the normal body cells [47]. Chemotherapy is mainly systemic and can be used separately and in combination therapies [5, 16]. Mode of their action, the chemical structure, homology, and composition are the main factors while choosing and following up of chemotherapeutic agents. While starting the therapy order of drug given, time for which it is given and dosage that is administered are very crucial steps [47].

1.8 Chemotherapeutic Agent

Alkylating agents cause direct DNA damage by halting cell division. The major treating cancers using alkylating agents are leukemia, myeloma, lymphoma, sarcomas, and Hodgkin's disease along with ovary, breast, and lung cancers [2, 3], The side effects include damage to bone marrow and rarely causing acute leukemia after 5–10 years of treatment. Based on similarities in mode of action platinum drugs are also included in alkylating agent's family with reduced chances of causing leukemia after treatment. Some examples are

- Platinum drugs (cisplatin, carboplatin, and oxaliplatin)
- Alkylating agents are nitrogen mustard (mechlorethamine, chlorambucil, cyclophosphamide, ifosfamide, and melphalan)
- Alkyl Sulfonate (busulfan)
- Trizines (dacarbazine, temozolomide)
- Ethylenimines: thiotepa and altretamine
- Nitrosoureas (streptozocin, carmustine, lomustine).

Another class is **antimetabolites** which are analogs for the unit of DNA and RNA and halt their growth specifically effecting the S phase of cell cycle [28]. They are used for treating leukemia, ovary, breast, and intestinal cancers. Few examples of this class includes

- 5-Fluorouracil (5-FU)
- 6-Mercaptopurine (6-MP)
- Capecitabine
- Cladribine
- Clofarabine
- Cytarabine
- Floxuridine
- Fludarabine
- Gemcitabine
- Hydroxyurea
- Methotrexate
- Pemetrexed
- Pentostatin
- Thioguanine.

Anthracyclines are another important class of chemotherapeutic agents that target DNA replication enzymes, effecting all phases of cell life cycle. Different tumors are treatable with this class but with a limitation of damaging the heart permanently, by inhibiting the topoisomerase II, leading to post treatment acute myelogenous leukemia, after 2–3 years in most cases if dosage limit reaches the upper level [46]. These are

- Daunorubicin
- Doxorubicin
- Epirubicin
- Idarubicin.

Other than anthracyclines, mitoxantrone is an anticancerous antibiotics which is comparable to doxorubicin due to their similar mode of action and effect on heart damage at high dosages [28].

Topoisomerase inhibitors, another class of chemotherapeutic agents that unwind the DNA and stop its replication. Both topoisomerase I and II have their inhibitors separately like topotecan and irinotecan for topoisomerase I and etoposide, mitoxantrone and teniposide for topoisomerase II [46].

Other naturally derived inhibitors such as plant alkaloids act as **Mitotic inhibitors** because they halt cell division at mitotic phase of cell cycle by inhibiting the protein synthesis. Lungs, breast, ovaries, lymphomas and leukemias can be treated with them [46]. With the high dosages, this class of chemotherapeutic agents can damage peripheral nervous system. Some examples are

- Taxanes: paclitaxel and docetaxel
- Epothilones: ixabepilone
- Vinca alkaloids: vinblastine, vincristine, and vinorelbine
- Estramustine.

There are some chemotherapeutic agents like L-asparaginase, bortezomib (proteasome inhibitors) which have uncommon mode of actions and are included in uncategorized chemotherapeutic agents [28, 43].

1.9 Angiogenesis Inhibitors

These inhibitors works differently by blocking the development of blood vessels inside the tumor tissue. Tumor cells require separate blood supply to fulfill their nutrition requirement and growth. Angiogenesis inhibitors do not kill the tumors rather starve them and block their growth resulting shrinkage of tumor mass by preventing new blood vessels to form [48]. Chemotherapeutic agents kill normal cells as well but angiogenesis inhibitor do not kill normal cells but they need to be administered for the longer time periods. Usually, they inactivate VEGF receptors by binding to them and ultimately the receptors to stimulate growth of new vessels around tumor mass. Some examples are thalidomide, interferon, bevacizumab (Avastin), cilengitide (EMD 121,974), and cediranib (Recentin VB-111) [11, 46].

1.10 Radiotherapy

In late nineteenth century, Becquerel and Rontgen had discovered X-rays which were beneficial for radiation treatment. The first cancer case was cured using radiation in 1898. Later, the progress was made in the procedure gradually enabling scientists to use rotational linac radiotherapy known as "Clinac6" in which these charged physical particles are propelled to move through a vacuum tunnel called linear accelerator or linac [4]. The development of modern computers enabled three-dimensional X-ray therapy like intensity-modulated radiation therapy (IMRT) using mapping information from Computed Tomography (CT) scans. Marie Curie research in radium introduces radiotherapy in medicine. Now it is a separate specialized field in cancer treatments [19].

Radiotherapy is linked to the use of physical particles like electrons, protons, and different ions following the mechanism that high energy radiations alter and stop the process of cell division and proliferation by damaging the genetic material. It can also shrink the tumor growth if given prior the surgery [8]. Also, it can shrink the left over tumor cells after surgery, thus reducing the relapse of cancer.

As mentioned, the physical particles are charged electrically in biological bodies upon incidence, and energy is transferred from the rays to the body cells through which it passes [4]. These radiations either can directly kill the cancer cells

or genetically alter them to accede to apoptosis and cell death. The mechanism involved in genetic alteration with radiation lies in the fact that damaged DNA do not replicate, halting cell division and proliferation, resulting in cell death [19].

During treatment the major adverse effect of radiation therapy is that it also effect the normal cell growth in the body, especially those lying close to the main tumor mass [49]. However, cancer cell lacks effective repair system as compared to normal cells that minimizes the net damage done as a result of radiation therapy.

1.11 Radiation-Based Surgeries

Gamma Knife Systems are not actual surgeries yet they use gamma beam light emission for treating tumors and sores. The radiation beam combines to concentrate on tumor cellular mass giving high radiation doses on the affected area without any incision [31]. **Stereotactic Surgery** ionizing radiations at high doses are focused and concentrated on the damaged area in the body non-invasively [31]. The focusing of radiations is very important and crucial otherwise the adjacent normal tissues to the tumor area also gets effected [25]. This technique is advisable for brain tumors especially when the surgeries are considered unsafe for patients. **Linear Accelerator Systems (LINAC)** are the one which utilize high energy X-rays for cancer treatment like Cyber Knife®, X-Knife®, Novalis®, and Peacock® [25]. Another method is **Proton Beam Therapy** that utilizes radiation beams and is considered as molecular radiation treatment. It includes X beams/gamma beams and particles like proton and neutrons [21].

1.12 Techniques Used in Radiation Therapy

Fractionation is based on the radiobiological difference between normal and cancer cells, as normal cells have better tendency to regrow and repair the damage by only sub-lethal dosage of radiation. **3D Conformal Radiotherapy** includes CT scan-based 3D radiation therapy, which is now one of the primary detection method for cancer masses in the body [22]. Another one is **Intensity Modulated Radiation Therapy** that utilizes inverse planning software for modulating radiation intensity during therapy. The irregular intensity dosage targets the tumor mass differentially and shrink their size gradually [38]. **Image Guided Radiotherapy** is a technique that helps in positioning the radiation correctly away from the critical body organs and toward the tumor mass avoiding incorrect aiming and thus damaging the nearby cells [39].

1.13 Hormonal Therapy

Recent advances have revealed that hormones play crucial role in growth and proliferation of cells. Hormonal disturbances cause malignancy in nearly 25% males and 40% females. Unlike chemotherapy, hormonal therapy causes no cytotoxicity; hence, very less side effects are associated with it (EBCTCG) [17]. This therapy can be a better choice while treating lymphoma, multiple myeloma, and leukemia. If given before the chemotherapy treatment, it can mitigate the hypersensitivity caused by chemotherapy, and if given after chemotherapy, it can relief the nausea and vomiting in the patients [46].

1.14 Immunotherapy

It includes the treatment with antibodies, dendritic cells, vaccines, and cytokines. It has added new dimensions to clinical practices. This treatment method is more specific, efficient, less toxic, and with minimal side effects. Immunotherapy kills tumor cells either directly or indirectly by activating human immune system against the tumor cells [32]. Other treatment methods like surgery, chemotherapy, and radiotherapy also affect the healthy cells of the body. However, antibodies are specific and show a very less toxic effect. This property has also encouraged the production of therapeutic antibodies [4]. The very first evidence was dated back to 1982 with a lymphoma patient while treating with mouse mAb directed against B lymphocytes. However, it is also revealed that some have developed anaphylactic reactions when administered repeatedly [4]. The larger size of antibodies causes immunogenicity along with differences in glycosylation pattern between murine and human Abs, leading to cessation of antibody use in therapy. Development of complete human Abs is harder to develop yet required to avoid immune rejection [26].

1.15 Nanostructure-Based Therapeutics

From past two decades, the nanostructure-based therapeutics and diagnostic agents have been introduced in cancer treatment [33].

The main purpose for this therapy is to deliver a therapeutic moiety to treatment site that is tumor cells, depending upon the required pharmacokinetics, in a controlled manner with reduced side effects and drug resistance [51]. Nanostructured materials may also be used to detect cancer cells based on their associated biomarkers.

The main advantages of these structures are ability for specific size synthesis and penetration to tumor cell surface. They can overcome physiological barriers, target tumor specific cell markers, increase plasma half-life of chemotherapeutic drug, drug protection from biological degradation and synthesis of multifunctional platforms for combined therapeutic applications (theranostic nanoparticles) [4].

The nanoparticles can be coupled with biological agents like folic acid. The major concerns while designing nanostructures are heterogeneous distribution of reactants, insufficient mixing, variations in their physicochemical characteristics, and various post-synthesis purification steps. Adaptive immune response is another major concern with the repeated application of nanoparticles [12, 29].

1.16 Miscellaneous Treatment Modalities

Hyperthermia or thermotherapy is one of the form of cancer treatments in which body tissues are heated at high temperature almost equal to 113 °F to damage and kill cancer cells with very little or no damage to the normal body cells [27].

Another form is photodynamic treatment for cancer in which a drug called a photosensitizing agent is activated by a laser light or light emitting from LEDs to kill cancer cells. The treatable cancers are pancreatic, esophageal, lungs, and non-melanoma skin cancers [14].

In gene therapy, new genes are introduced into cancer cells or their surrounding tissues to cause cell death or slow down the cancer cell growth. It is a flexible technique in which wide range of genes can be introduced in cells using vectors to respond to various chemical or physical stimulants either internally or eternally to deliver therapeutic gene to the cell nuclei [45].

Various gene therapies, hyperthermia, and photodynamic treatments use engineered nanomaterials. They can be used in isolation or in combination to treat cancers.

Cancer development is also associated with viruses, and almost 15% of malignancies are associated with oncogenic viruses like human papillomaviruses, Epstein–Barr viruses, herpes virus, and hepatitis B & C virus [36]. Recent studies have revealed that related studies of these causative agents will help in understanding initiation and spread of cancer in the body [37].

Stem cell therapy is one of the options for cancer treatment as these are the undifferentiated cells in bone marrow and has the ability to differentiate into any type of cells in the body [40]. This therapeutic method is still under clinical trials. Mesenchymal stem cells are currently under use in these trials [46].

1.17 Conclusion

Cancer is still a threat to human lives and still it has high prevalence in human population. It involves complex alterations in morphological and physiological condition of the body. It is still a challenge to find a complete remedy, yet there are different treatment modalities used for curing cancer. Some are effective in certain type and stage of cancer yet some still have few side effects.

Throughout this book different treatment modalities are discussed with their effectiveness and side effects. Radiotherapy, immunotherapy, hormonal therapy, surgeries, chemotherapy, personalized medicine approach, gene therapy, viral

oncotherapy, nutritional assessments, psychological care for cancer patients, nanostructure practices, and some others.

However, it is much clear that fighting cancer will not be very easy task due to complex nature of cancer spread.

Although these new treatment modalities may open new era as a hope for so many cancer patients. As we proceed in this book, different modalities are discussed.

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