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Different types of Cancer treatment, its advancement, benefits, and side effects

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Abstract

Cancer is one of the most leading causes of death by a disease. With the advancement of research and technology, increasing awareness and understanding, the diagnosis and treatment of cancer continue to advance while the challenge for cure remains. Cancer is the first or second leading disease that causes premature death in 134 of 183 countries and one in six deaths in the world is due to cancer. The lung cancer is considered as most common cancer with 11.6% of all cases while female breast cancer and colorectal cancer stands at 2nd and 3rd most common cancers with 11.6% and 10.2% respectively. Year after year, the rate of cancer continues to increase.

WHOs latest report (https://medicineworld.org/cancer/history) suggested that the number individuals affected and the dead by caused by cancer will nearly double in the next 20 years. Finding a cure for cancer is an urgent need in this world. This review is focused on the currently available different types of cancer therapies, benefits of the treatment and sides effects.

Keywords: Cancer; Leading Cause of Death; Therapies; Side Effects

1. Introduction

The latest report on cancer facts and figures estimated that, in 2022, roughly 20 million people were newly diagnosed with cancer and 9.7 million people died from cancer worldwide. Based on the population growth, the number of cancer cases is projected to increase up to 35 million, by 2050 [2]. The chance of developing cancer is very high as 1 in 5 individuals is expected to develop cancer in their lifetime while 1 in 9 males and 1 in 12 females is expected to die from the disease (GLOBOCAN 2022: gco.iarc.fr/today/). When all types of known cancers are combined, globally the incidence rate is about 213 in 100000 individuals among males and 186 in 100000 individuals among females (GLOBOCAN 2022: gco.iarc.fr/today/). Subsequently, mortality rate is 110 in 100000 individuals in males whereas 77 in 100000 individuals in females. The incidence of cancer and the deaths due to cancer is higher among males than in females (GLOBOCAN 2022: gco.iarc.fr/today/), this is because more males are indulged in tobacco smoking, alcohol consumption, and higher risk of having chronic hepatitis B and C infections (liver cancer). However, in few cancer types such as breast, thyroid, and gallbladder cancers, the incidence is more in females than the males; for example, thyroid cancer incidence rate is 3 times higher in females, which is believed largely due to differences in health care utilization and overdiagnosis [3]. In males, the mortality rate is highest in lung cancer patients whereas, in females, breast cancer causes most mortality. Over the years several types of treatments for cancer have been developed including the use of plant derived compounds [4] and several patents have benefited from those treatments. However, there is no cure available for cancer until today, and it is unlikely to find a cure for the disease soon. Therefore, much further research is necessary to find better treatment and find cure for cancer.

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2. Conventional treatments for cancer

A breakthrough of understanding cancer from ancient knowledge to the modern concept came from the discovery of the first tumor viruses (wart viruses: presently known as papilloma viruses) by Vilhelm Ellerman and Olaf Bang in 1908 [1,5] and Peyton Rous in 1911 [6,7] that can be transmitted in chickens. The highly impacted work had not been appreciated until 40 years later [8,9,10]. Ellerman and Bang's, and Rous's discovery began to influence after the identification of mammalian tumor viruses by Richard Shope and John Bittner in the 1930s, and by Ludwik Gross in the 1950s [9]. Even though the cancer has been identified before the time immemorial, 3000 years before the Lord Jesus Christ was born, identification of causing agents came to achieve much later. Notably, in the beginning of 1900 external agents like chemicals, radiation and viruses had been accepted as etiological factors in cancer [1,11,12,13,14,15,16]. It happened as a surprise finding when both chemical and viral carcinogenesis generated the same results [17]; because the two, independently, evidenced the correlation between tumors and mutated genes. With the more advanced understanding of cancer, finding ways for cure and appropriate treatment continue to progress with time. While a true cure for cancer is yet to be found, better treatments are available with the development of advanced technology and medicine.

In ancient days, hundreds of years before Christ, Hippocrates (ca. 460 – ca. 370 BC) the Greek physician who is being honored as the Father of Medicine, summarized his recommendations for the treatment of cancer, stating that tumors which are not cured by medicine are cured by iron (knife), those which are not cured by iron are cured by fire (cautery), and those which are not cured by fire are incurable [1,18,19,20,21,22]. In the case of occult or deep-seated tumors, he advised not to use any treatment because if applied any treatment at that point, the patient would die quickly, whereas, without treatment, the patient might survive for an extended period [20,23]. The ancient treatment for cancer was carried out with cautery, knife, or salts of lead and sulfur or arsenic paste etc. Until the 19th century sulfur or arsenic paste were used as "Egyptian ointment" [1,23,24]. It may be noted that surgical treatment has been existed even earlier as description of the cautery destruction of the breast was recorded in the Egyptian papyri dating back to 1700 B.C [1,25]. The Roman encyclopaedist, Aulus Cornelius Celsus recommended that superficial carcinomas should be treated first with a topical application of cabbage, a salted mixture of honey and egg white, or ripe fig [26]. On the other hand, Galen of Pergamon suggested that the accumulation of black bile could be prevented by using purgatives [1,18,24,27]. Moreover, he also recommended using ointment made from poppy heads for healing the pain in terminally ill individuals [27,28].

In the course of time, the use of microscopy in pathology during the early 19th century had replaced the gross descriptive pathology of cancer of the 18th century. The advance developments in pathology and surgery between 1500 and 1750 had driven in the further progress of the 18th and 19th centuries in understanding the nature and the macroscopic and microscopic composition of benign and malignant tumors [27,28]. The conventional treatment methods for cancer include surgical therapy, hormone therapy, radiation therapy, chemotherapy, immunotherapy and targeted therapy etc.

2.1. Treatments by surgery

The main purpose of surgical treatment for cancer is to remove the entire tumor contained in one area, or partial removal of the tumor (when entire removal might damage an organ or the body) which can help other treatments work better or removing the tumors that cause pain [31]. Over the time, with increased knowledge of cancer from genetics, molecular biology, and the tumor immunological point of views in parallel with the advancing technologies, the use of surgery in cancer treatment has been dramatically changing and broadens its role over the past century. Earlier surgery was considered as the only chance treatment for cure of cancer and historically surgery was the first line of defense against a tumor; however, the increased use of neoadjuvant therapies has often shifted surgery to a second or third line of treatment [1,32]. The role of surgery does not confine to a purely therapeutic manner but also included considerations of both palliation (pain, bleeding, obstruction, malnutrition, or infection) and prophylaxis (e.g. use of tamoxifen for the chemoprevention of breast cancer) and the surgeons have cemented their role as physician-scientists, investigating novel molecular and immunologic therapies [32]. With the knowledge of genetic predisposition to cancer, the surgeon removes healthy organs to prevent malignancy. Advancing imaging technologies has also possibly reduced the need for surgical intervention for staging such as in Hodgkin's lymphoma. However, expansion of neoadjuvant therapies often requires surgical interventions to accurately assess response to therapy. On the other hand, harvesting tumors is necessary for molecular staging as well as identifying molecular targets for specific therapies. And thus, surgery in cancer therapy has multidisciplinary roles to play apart from therapeutic application of established tumors but also towards the prevention of cancer.

Nowadays, with more advanced techniques surgery that can be performed without involving cuts with scalpels have been developed including cryosurgery, lasers, hyperthermia, and photodynamic Therapy [32]. In Cryosurgery the

extreme cold produced by liquid nitrogen or argon gas is used to destroy abnormal tissue. Early-stage skin cancer, retinoblastoma, and precancerous growths on the skin and cervix may be treated by cryosurgery. Laser treatment uses powerful beams of light to cut through tissue and it may be used to shrink or destroy tumors or growths that might turn into cancer. It is also used to treat tumors on the surface of the body or on the inside lining of internal organs such as basal cell carcinoma, cervical changes (which has possibility to become cancer), and cervical, vaginal, esophageal, and non-small cell lung cancer etc. Hyperthermia treatment is carried out by exposing areas of body tissue to high temperatures to damage and kill cancer cells or make them more sensitive to radiation and certain chemotherapy drugs. At present, this treatment is not widely available as clinical trials for the treatment are in progress. Radiofrequency ablation is a kind of hyperthermia that uses high-energy radio waves to generate heat. In case of Photodynamic therapy drugs which react to a certain type of light are used to expose the tumor. These drugs become active and kill nearby cancer cells and this therapy often used to treat/relieve symptoms caused by skin cancer, mycosis fungoides, and non-small cell lung cancer etc.

2.2. Treatments using hormonal therapy

Hormones are signaling molecules which may be proteins or substances that are transported to distant organs to regulate cell function, physiology and/or behavior of the body, and it is synthesized by different organs/glands in the body of all multicellular organisms [33,34,35]. Different hormones play different functions of the body, and some cancers depend on hormones for their growth. Therefore, blocking or alteration of hormone functions can help in slowing or stopping the growth of tumors. Treating cancer with hormones is mostly used in certain kinds of breast cancer and prostate cancer that depend on sex hormones to grow. Hormone therapy is considered a *systemic* treatment because the drugs that are used for targeting hormones circulate throughout the body to find the hormones. Such treatments are called *local* treatments because they affect one part of the body. Surgeries are also performed for removing hormones producing organs.

Hormone therapy can help the cancer patient in several ways such as in lessening the chance of returning of the cancer or in stopping or slowing down of its growth and to reduce cancer symptoms. In the case like men with prostate cancer who are not able to have surgery or radiation therapy, hormone therapy may be used to reduce or prevent symptoms of cancer. Hormone therapy works in two large groups, one group with those having blockage of the body's ability to produce hormones and the other having interfere with how hormones behave in the body. This therapy is used for treating prostate and breast cancers that use hormones to grow and are often used along with other cancer treatments. The therapy is practiced in many ways that include oral pills that are given through mouth, injection into a muscle in the arm, thigh, or hip, or right under the skin in the fatty part of the arm, leg, or belly or by surgery which removes organs that produce hormones (e.g., removal of ovaries and testicles in women and men respectively). However, there are also concerns of side effects of hormone therapy that include, hot flashes, weakened bones, diarrhea, Nausea, fatigue etc. [35]. One of the most encountered clinical situations in hormone replacement therapy is regarding the relief of menopausal symptoms of breast cancer survivors [36]. This menopause can be resulted from either chemo- or radiotherapy, or some type of antiestrogenic endocrine therapy. Therefore, the guideline of the International Menopause Society stated 'no hormone replacement therapy' should be given to these patients, but non hormonal methods such as changing lifestyle, behavioral therapy, gabapentin, venlafaxine or fluoxetine to be preferred [37,38]. Based on the available reports hormone replacement therapy is advantageous to such cancers like endometrial cancer type I, cervical adenocarcinoma, hematologic malignancies, local cutaneous malignant melanoma, colorectal cancer, hepatocellular cancer; and neural with BRCA 1/2 mutation carriers without cancer, endometrial cancer type II, uterine carcinosarcoma and adenosarcoma, certain types of ovarian cancer, cervical, vaginal and vulvar squamous cell carcinoma, prolactinoma, kidney cancer, pancreatic cancer, thyroid cancer; but relatively contraindicated for various reasons with leiomyosarcoma, certain types of ovarian tumours, brain tumours, advanced metastatic malignant melanoma, lung cancer, gastric cancer, bladder cancer; and disadvantageous and contraindicated with breast cancer, endometrial stroma sarcoma, meningioma, glioma, hormone receptor positive gastric and bladder cancer etc. [36].

2.3. Treatment by radiation

Radiation therapy or radiotherapy for cancer uses ionizing radiation to control or kill malignant cells and normally delivered by a linear accelerator. It uses high doses of radiation to kill cancer cells and shrink tumors; low doses are used in x-rays to see inside the body, as for x-rays of the teeth or broken bones. Radiation therapy may be curative for several cancer types if localized to one area of the body. It may also be used as part of adjuvant therapy, to prevent tumor recurrence after surgical removal of primary malignant tumor (for example, early stages of breast cancer and pancreatic cancer) [39,40,41]. Radiation therapy is synergistic with chemotherapy, and in susceptible cancers, it has been used before, during, and after chemotherapy and often accompanied with other cancer treatments, such as surgery, chemotherapy, and immunotherapy [35,42].

Radiation therapy does not kill cancer cells right away but takes days or weeks of treatment before the DNA damaged reaching a sufficient level for cancer cells to die [43,44]. When the DNA damaged reaches beyond repair, stop dividing or die; the cancer cells die or broken down, then removed by the body [44]. This therapy is commonly applied to tumor cells because of its ability to control cell growth. The ionizing radiation works by damaging the DNA of the cancerous cells leading to death. Along with the tumor cells, the radiation killing may also include draining of lymph nodes if they are clinically or radiologically involved with the tumor or suspected of risk for subclinical malignant spread [35,45]. Further, the radiation fields need to cover a margin of normal tissue around the tumor to avoid the uncertainties in daily set-up and internal tumor motion that may be caused by internal movement due to respiration and bladder filling and movement of external skin marks relative to the tumor position. The types of radiation therapy that would apply to cancer cells depends on many factors that include the type of cancer, tumor size, tumor location in the body, tumors closeness to normal tissues that are sensitive to radiation, general health, and medical history of the patient, whether other types of cancer treatment would be required, age and other medical conditions etc [35].

Radiation therapies are grouped into two major kinds, i.e., external beam and internal radiation therapy. In the case of external beam radiation therapy, the radiation does not touch the body but can move around the body, sending radiation to a part of your body from many directions. This therapy is used for local treatment that is to treat a specific part of the body, such as cancer in the lung that has radiation only to the chest and the whole body. Whereas, for internal radiation therapy, the radiation source can be solid, or liquid is placed inside the body. For solid radiation therapy (also known as brachytherapy), seeds, ribbons, or capsules that contain radiation are placed in the body as source of radiation, within or near the tumor; and this therapy is used for local treatment. In case of liquid radiation therapy (also called systemic therapy), radioactive drugs such as radiopharmaceuticals or radionuclides are used as source of radiation; this treatment travels in the blood to tissues and throughout the body seeking out and killing cancer cells. During systemic radiation, body fluids, such as urine, sweat, and saliva, give off radiation for a while. Radiation can cause side effects such as making it hard to eat, nausea, mouth sores, and throat problems to the patients [35].

Different cancers respond to radiation therapy in different capacities [35,46,47]. Highly radiosensitive cancer cells such as of leukemias, most lymphomas and germ cell tumors are rapidly killed by modest doses of radiation. Majority of epithelial cancers are only moderately radiosensitive, and require a significantly higher dose of radiation (60-70 Gy) to achieve a radical cure. Some types of cancers like renal cell cancer and melanoma are notably radioresistant, they require much higher doses to produce a radical cure than may be safe in clinical practice. However, radiation therapy is still a palliative option for many patients with metastatic melanoma. Combining radiation therapy with molecular targeted therapy and immunotherapy is an active area of investigation and has shown promising results for melanoma and other cancers [48,49,50,51].

2.4. Treatments using chemotherapy

Chemotherapeutic treatment for cancer uses one or more anti-cancer drugs (chemotherapeutic agents) to stop or slow down the growth of cancer cells that grow and divide quickly, lessen the chance of cancer to return, ease cancer symptoms, shrink tumors that are causing pain and other problems etc. Chemotherapy implicates the use non-specific intracellular poisons to inhibit mitotic cell division or induce DNA damage and thereby inhibition of DNA repair can enhance chemotherapy [52]. In the past attempts for improving treatment efficacy, by inventing various combinations of cytotoxic agents, have given disappointing results with significant mortality [53]. However, in the recent years, cancer treatment with chemotherapy is becoming more and more advantageous in specifically targeting and killing tumor cells without affecting healthy cells. This revolution gives the potential for improving treatment efficacy and tolerability in the treatment of cancer and ultimately improving patient outcomes [54]. A considerable improvement has been resulted when treatment was carried out combining new targeted therapies and existing chemotherapy. Introduction of targeted therapies such as ‘imatinib’ (a tyrosine kinase inhibitor) for chronic myeloid leukemia and gastrointestinal stromal tumor, or ‘erlotinib’ (an inhibitor of the epidermal growth factor receptor tyrosine kinase) for lung cancer with other targeted therapies that include antibodies that recognize cell surface markers which trigger an immune response or stop signal cascades, had provided better outcomes to the patients [55]. It is one of the major categories of the medical discipline specifically devoted to pharmacotherapy for cancer known as medical oncology [56,57]. Like the other therapies of cancer, chemotherapy treatment is often accompanied with other cancer treatments, and it is used to treat various types of cancer [35]. Tumors are made smaller before surgery or radiation therapy by chemotherapy which is known as *neoadjuvant chemotherapy*. It also destroys cancer cells that may remain after surgical or radiation therapy which is called *adjuvant chemotherapy*. Since chemotherapy not only kills or slow down fast-growing cancer cells, but also healthy cells that grow and divide quickly such as cells that line in the mouth/intestines and those that cause hair growth. It may cause side effects such as mouth sores, nausea, and hair loss; but often become better or go away after the chemotherapy is finished (one receives chemotherapy every day for 1 week followed by 3 weeks with no

chemotherapy, total 4 weeks make up one cycle). The most common side effect is fatigue. Chemotherapy can be given orally, Intravenous (IV)/ Intrathecal/ Intraperitoneal (IP)/ Intra-arterial (IA) injection or in the topical form [35].

2.5. Treatments with immunotherapy

Cancer treatment by immunotherapy (immuno-oncology) works with artificial stimulation of the immune system, by improving the function of natural immune system in fighting the disease. Cancer immunotherapy takes advantage of the cancer cells that often have tumor antigens (proteins or other macromolecules like carbohydrates), that can be detected by the antibodies of the immune system. On the contrary to normal antibodies that bind to external pathogens, the modified immunotherapy antibodies bind to the tumor antigens which mark and identify the cancer cells for the immune system to inhibit or kill. Two renowned immunologists, James P. Allison and Tasuku Honjo received the Nobel Prize in Physiology or Medicine in 2018 for the discovery of cancer therapy that works by inhibiting the negative immune regulation [58]. Immunotherapy may be considered as biological therapy as it uses the substances made from living organisms such as white blood cells, organs, and tissues of the lymph system. It detects and destroys abnormal cells and may prevent or curb the growth of many cancers [37,59]. For example, immune cells are sometimes found in and around tumors (which are known as tumor-infiltrating lymphocytes or TILs) are signs of immune system responding to the tumor. In fact, cancer patients whose tumors contain TILs often do better than those whose tumors do not have TILs [37]. On the other hand, even though the immune system can prevent or slow the growth of cancer, cancer cells have ways to avoid destruction by it. For example, cancer cells have genetic changes making them less visible to the immune system, their surface proteins can turn off immune cells and change the normal cells around them and thereby interfering with the way of immune system responding to the cancer cells [37]. There are several types of immunotherapy for cancer that include 1) immune checkpoint inhibitors which are drugs that block immune checkpoints, 2) T-cell transfer therapy that uses monoclonal antibodies prepared in the lab are designed to bind to specific targets on cancer cells, 3) treatment vaccines which work by boosting the immune system's response to cancer cells, 4) immune system modulators which enhance the body's immune response against cancer etc. [37,60,61,62,63,64,65,66]. Immunotherapy drugs have been approved to treat many types of cancers; nonetheless, it is not yet used widely like surgery, chemotherapy, or radiation therapy [37,62]. Immunotherapy can cause side effects and toxicity due to the immune system that has been revved-up to act against the cancer also acts against healthy cells and tissues in the body [37] and toxicity relating to the mechanisms of action depending on the type of therapy, respectively [67,68,69]. Depending on the type of cancer and health condition of the patients, the treatment may be given every day, week, or month; in some cases, in cycles which are a period of treatment followed by a period of rest. The rest period gives a chance for the body to recover and respond to immunotherapy and to build new healthy cells. The testing of combinations of immune checkpoint inhibitors and other types of immunotherapies, targeted therapy, and radiation therapy to overcome resistance to immunotherapy are in progress [62]. According to recent reports, only a small portion of people who receive immunotherapy will respond to the treatment and therefore finding ways to predict which people will respond to treatment is a major area of research [37,60]. The learning more about how cancer cells evade or suppress immune responses against them and better understanding of how cancer cells get around the immune system could lead to the development of new drugs that block those processes.

2.6. Treatments by targeted therapy

Targeted therapy is devised to target the proteins that control the regulatory system for growth, division and spreading of cancer cells; and it is the foundation of precision medicine. Targeted therapy, which is also known as molecularly targeted therapy is one of the major modalities of medical treatment for cancer [70,71]. Targeted therapy works by interfering the specific targeted molecules needed for carcinogenesis and thereby blocking the growth of cancer cells rather than simply interfering with all rapidly dividing cells unlike the other therapies such as traditional chemotherapy [72,73]. There are two main approaches to achieve target therapy, direct and indirect approaches. In direct approach specific cell signaling events are altered through monoclonal antibodies or small molecules inhibitors [74]. Indirect approaches use the molecular targets which are overexpressed or exclusively expressed on the surface of tumor cells, to send cytotoxic molecules (such as chemotherapeutic agents, toxins, cytokines, or radionuclides) that can be conjugated to monoclonal antibodies or peptide ligands via a chemical linker or nanocarriers, decreasing the peripheral toxicity [74,75,76,77]

A clear understanding about the changes of DNA and proteins that drive cancer will be able to provide better guidance in designing promising treatments for targeting these proteins. Most of the targeted therapies use either small-molecule drugs or monoclonal antibodies [37,72]. The small-molecule drugs are designed to be small enough to enter the cells easily and attach to specific targets inside the cancer cells, and the monoclonal antibodies are the therapeutic antibody proteins produced in the lab [37]. While, some monoclonal antibodies mark cancer cells allowing them to be seen better and be destroyed by the immune system, others directly stop cancer cells from growing or cause them to self-destruction or carry toxins to cancer cells, effective targeted treatments based on the changes in the molecular biology

of the tumor cells are designed to block biologic transduction pathways and/or specific cancer proteins to induce the death of cancer cells by means of apoptosis and stimulation of the immune system, or specifically deliver chemotherapeutic agents to cancer cells, minimizing the undesirable side effects [72,73,74,75,76,77,78]. Some of the new therapies are focused on transporting the chemotherapeutic agents to tumors, avoiding normal tissues, and reducing toxicity in the rest of the body, but also protect cytotoxic drugs from degradation, increase the half-life, payload and solubility of cytotoxic agents and reduce renal clearance.

The targeted therapies work in many ways [37]- 1) it helps to destroy the immune system of cancer cells (cancer cells thrive as their immune system differs from the bodies' immune system). Certain targeted therapies can mark cancer cells and make it easier for the immune system to find and destroy them while others help in boosting the body immune system to fight better against cancer; 2) uncontrolled cell divisions are stopped. Healthy cells of the body usually divide to make new cells only when they receive strong signals to do so. However, some cancer cells change in their surface proteins allowing them to divide whether signals are present. In this case, some therapies can interfere with these proteins, preventing them from the stimulation of uncontrolled division; 3) stops signals that helps in forming blood vessels. New blood vessels (angiogenesis) are required for tumors to grow beyond a certain size, which are formed in response to signals from the tumor. Targeted therapies called angiogenesis inhibitors can interfere with these signals to prevent a blood supply from forming and thereby tumors remain small. In case a tumor already has a blood supply, these treatments can cause blood vessels to die, leading the tumor to shrink; 4) delivers cell-killing substances to cancer cells. There are monoclonal antibodies that can combine with toxins, chemotherapy drugs, and radiation, then, attach to targets on the surface of cancer cells; the cells take up the toxic substances causing them to die, while the cells without the target site are not harmed; 5) cause cancer cell death. Healthy cells die in an orderly manner when they are damaged or are no longer needed. But cancer cells have ways to avoid this process of dying. There are targeted therapies that can direct cancer cells to go through the orderly process of cell death; 6) starving hormones that needs by cancers cells to grow, as in some breast and prostate cancers. In such case hormone therapy (which is a type of targeted therapy) can work in two ways, by preventing the body from making specific hormones or preventing the hormones from acting to the body cells, including cancer cells.

Depending on the patient's condition, the treatment can be every day, every week, or every month. Some targeted therapies are given in cycles that include a period of treatment followed by a period of rest. However, like the other therapies, targeted therapies also have drawbacks in such as cancer cells can become resistant to targeted therapy and therefore combined used of different targeted therapies may work best or with other cancer treatments, such as chemotherapy and radiation [37,72]. The most common side effects of targeted therapy include diarrhea and liver problems. Other side effects might be the problems with blood clotting and wound healing, high blood pressure, fatigue, mouth sores, nail changes, the loss of hair color, and skin problems. In the very rare case, a hole may form through the wall of the esophagus, stomach, small intestine, large bowel, rectum, or gallbladder [37].

3. Differentiation therapy for cancer

Differentiation therapy is one of the emerging therapies for cancer which uses potentially lesser toxic approaches that can modify cancer cell differentiation. This approach is based on the tacit assumption that many neoplastic cell types exhibit reversible defects in differentiation, which upon appropriate treatment, results in tumor reprogramming and a concomitant loss in proliferative capacity and induction of terminal differentiation or apoptosis (programmed cell death) [79]. There is a subpopulation of tumor cells with distinct stem-like properties that have been found responsible for tumor initiation, invasive growth, and metastasis formation, known as cancer stem cells [80]. The cancer stem cells generated tumors only from a small number of cells, whereas differentiated cancer cells do not [81]. The main characteristic of cancer stem cells is the ability to self-renew and differentiate into multiple types of cancer cells, and several other distinct tumorigenic abilities including stem cell signal transduction, tumorigenicity, metastasis, and resistance to anticancer drugs that are regulated by genetic or epigenetic changes [81,82]. Differentiation therapy for the treatment of cancer strengthens malignant cells to differentiate into more mature forms using pharmacological agents and thereby stopping them from becoming tumorous. It directs the self-renewing cancer stem cells, as well as their progeny transit amplifying cells to mature to terminal differentiation by force [83]. This therapy had come to a hallmark success after achieving effective results in the treatment of acute promyelocytic leukemia, neuroblastomas and myeloid leukemias. Cancer stem cells maintain their self-renewal capacity by activating multiple stem cell signaling pathways and inhibiting differentiation signaling pathways during cancer initiation and progression, like the normal adult stem cells involving in various developmental processes and tissue homeostasis [80]. Many recent studies have focused on targeting cancer stem cells to eradicate malignancies through the regulation of stem cell signaling pathways and the results of some of those studies have reached preclinical and clinical trial stages. Some of the drugs that are being used in differentiation therapy are retinoic acid (RA) for teratocarcinoma and neuroblastoma, RA in combination with arsenic for acute promyelocytic leukemia, histone deacetylase (HDAC) inhibitors in combination with RA in

neuroblastoma, RSPO3 (r-spondin 3) inhibitors for PTPRK (receptor-type tyrosine-protein phosphatase-κ)–RSPO3 driven colon cancer, vitamin D3 for acute myeloid leukaemia etc. [82].

4. Conclusion

Currently, many therapies are available for treating different types of cancer. However, there is major lake of precision and severe side effects and there is no cure, even though the treatment of breast cancer has greater chances of success if treated early but the long lasing side effects need to be kept into account. Cancer being at the 6th rank on rate of deaths globally caused by a disease, the disease is one of the biggest major health issues in the world. Every research towards finding the best treatments for the cure of cancer should always be strengthened and supported.

Compliance with ethical standards

Disclosure of conflict of interest

Authors have no conflict of interest.

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