Chemotherapy Effects on Immune System 13

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Abstract

The primary goal of conventional anticancer drugs always has been killing the tumor cells in the body. Cancer growth starts with certain irreversible changes within the immune system, and this in turn gave rise to the concept that tumor growth can be halted only by destroying the malignant cells. However, with the advent of targeted chemotherapeutic agents, drugs that specifically suppress cells promoting tumor growth and stimulate the immune system to act against the cancer cells, the management of cancers took a novel approach. Various conventional chemotherapeutic agents also have showed immune modulatory effects in recently conducted studies. Thus, targeting the immune system rather than the cancer cell seems to be a new and better perspective in cancer treatment.

Keywords

Chemotherapy · Immune system · Immune surveillance · Chemotherapeutic agents

13.1 Introduction

Cancers have been known to develop due to an imbalance of genes which promote development of tumor cells (proto-oncogenes) and genes which suppress the growth of tumor cells (tumor suppressor genes) (Hanahan and Weinberg 2000). In the physiological state, a delicate balance between these two prevents cancerous transformation of vulnerable cell in the body. There are many triggers that can lead to disruption of this balance ranging from sudden changes in the gene structure (genetic

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S. K. Basu et al. (eds.), *Cancer Diagnostics and Therapeutics*,
https://doi.org/10.1007/978-981-16-4752-9_13

mutations) or certain infections like human papillomavirus causing cervical cancer or exposure of the body to certain substances or chemicals that can lead to subsequent development of cancers (carcinogens) like cigarette smoke.

From the belief that no child with leukemia has ever been cured (Walker 1964) to the use of cell lines and targeted drugs for curing cancers, cancer chemotherapy has traversed great leaps. Surgery and radiotherapy were considered the mainstay in treating cancers up to the 1960s. However, cure rates plateaued despite development of more and more localized surgeries (DeVita and Chu 2008). As knowledge about behavior and properties of cancer cells expanded, it became clear that no single treatment modality would be sufficient for treating cancers. Thus, the management of malignancies gradually started involving interplay of surgery, radiotherapy, and chemotherapy.

13.2 The Immune System and Cancer

As the human body is exposed to a large number of bacteria, viruses, fungi, parasites, and other antigens on a daily basis, the immune system is responsible for the overall protection of the body. Immune response is the reaction of the above system toward averting any infection that can be detrimental to the body (Chaplin 2010). The immune system is of paramount importance in cancer patients because:

The disease *per se* can affect the immune system by destroying the bone marrow responsible for production of immune cells in the body.

Agents aiding in cancer treatment can in turn destroy the bone marrow, thereby weakening the immune system of the body.

A stronger immune system can forge a better fight against any kind of cancer.

White blood cells (WBCs) are responsible for development of immunity in the body. They are produced in the bone marrow. Cancer: Once it affects the bone marrow, or cancer drugs used to treat the disease can suppress the normal functioning of the bone marrow, thereby inhibiting proper functioning of WBCs. However, bone marrow suppression caused by antitumor agents is reversible most of the times and gets corrected once the drug is discontinued.

There are two kinds of immunity as depicted Fig. 13.1.
Innate immunity—immunity present since birth;
Acquired immunity—immunity that develops during growth of the person.

Innate immunity can be provided by anything ranging from the skin, acid in the stomach, and hair to neutrophils (a specific kind of WBCs) (Chaplin 2010). The components of innate immunity are always ready to attack any intruder into the body. They are the first-line defense against any infection. Acquired immunity, on the other hand, is something the body learns and slowly develops. The learning happens either because of a previous infection or vaccination. Once a particular infection is introduced into the body, the body remembers to recognize it the next

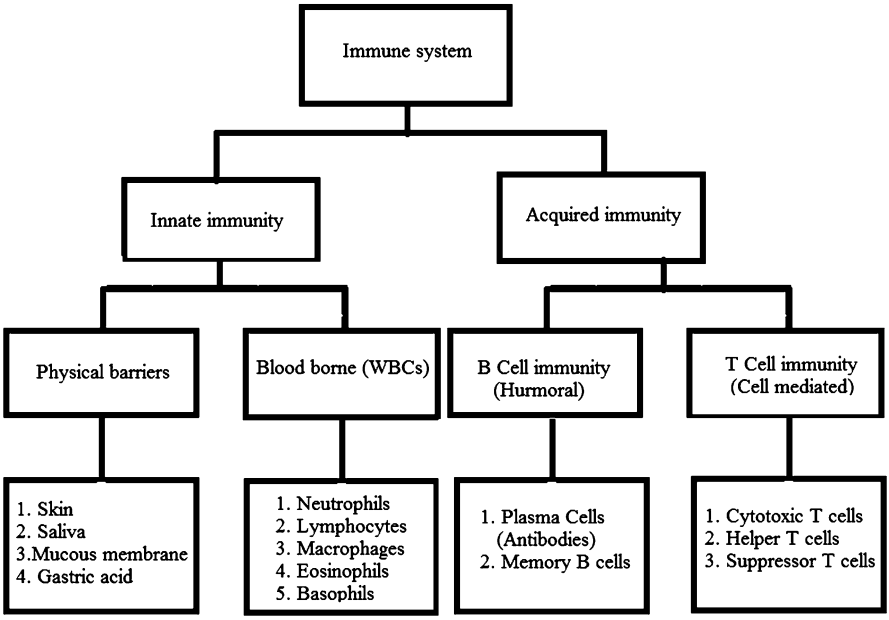

Fig. 13.1 Immune system

time a similar infection occurs and reacts in a timely manner to stop the infection from spreading.

Skin, tear, mucosa of the eyes, nose, and mouth form a shield against entry of possible germs or toxic substances into the body. Cancers or anticancer drugs can breach the innate immunity and thus make the body more susceptible to various infections. Once the physical barrier is breached and the germ or toxic substance enters into the body, the body deals with them through the WBCs, antibodies, and complement system present inside the body. They can either be already present within the body or are produced once the harmful substances enter the body.

Lymphatic system is the next line of defense that faces the infective organisms. It consists of lymph nodes present ubiquitously throughout the body. Lymph nodes secrete lymph, a clear fluid which essentially is blood plasma minus the red and white blood cells. The germs on entering the cells are filtered and drained by the lymphatic fluid, and they eventually make their way to the lymph nodes (Chaplin 2010). Swollen lymph nodes that can be felt during an infection or fever are thus a good sign of the body fighting the infectious organism. Conversely, swollen nodes in a cancer patient might indicate the disease progression to the next stage.

Organisms that escape the lymphatic system are then attacked by the next line of defense, the antibodies. Antibodies are produced in the WBCs and are highly specific; a particular kind of toxin or organism (antigen) has a specific type of antibody acting against it. They are also called immunoglobulins and are of 5 types—IgG, IgM, IgA, IgE, and IgD. Besides antibodies, the body produces a vast array of compounds like interleukins (ILs) and tumor necrosis factor (TNF) in the neutrophils (Chaplin 2010) and interferons that are part of the immune system and are circulated throughout the body in the eventuality of any kind of infection.

White blood cells or WBCs are produced in the bone marrow from stem cells and are one of the primary components of the immune system. There are three types of WBCs in the body—granulocytes (further divided into neutrophils, basophils, and eosinophils), lymphocytes (subdivided into B cells formed in the bone marrow and T cells formed in the thymus), and monocytes which can form macrophages.

Neutrophils: These are the most abundant type of WBCs seen in the circulation. They have a very short life span (few hours). In case of a cut, scratch, or aggregation of any kind of infective organisms within the body (like urinary or respiratory tract infections or skin infections), neutrophils are the first cells which are recruited in the concerned area. Once neutrophils infiltrate the wound or the infected tissue, they engulf the infective organism by a process called phagocytosis (Kennedy and DeLeo 2009) and release further enzymes to prevent the spread of infection into the surrounding tissues.

Eosinophils and basophils: They are much less abundant than neutrophils in the circulation. Eosinophils are predominantly associated with protecting the body against parasitic infections (Chaplin 2010). Basophils are associated with release of histamine, a substance released in the eventuality of an allergy of any kind.

Lymphocytes: They are responsible for protecting the body against majority of the bacterial and viral infections. Although production of lymphocytes starts in the stem cells as all other WBCs, the differentiation either completes in the bone marrow itself or spleen (B cells) or in the thymus (T cells). B cells further divide into plasma cells which then go on to produce antibodies that eliminate various foreign objects that enter into the circulation. Apart from helping in antibody production, B cells also have a memory of infective agents that have invaded the body previously so that future infections can be prevented. T cells are of three types—killer cells that kill various infected cells and prevent the spread of infection or tumor inside the body, helper cells that aid in the production of antibodies by the B cells, and suppressor cells that help in controlling the overall immune response by B cells and killer T cells.

Monocytes: Once formed in the bone marrow, they enter into the cells of the body and get converted into macrophages, which as the name suggests are the largest of all WBCs. They are omnipresent throughout the body and are responsible for clearing up the debris after neutrophils have phagocytosed the infective organisms. Macrophages persist for longer duration of time at the site of inflammation and thus play an important role in chronic inflammation (Chaplin 2010).

Major histocompatibility complex (MHC) (also known as the human leukocyte antigen (HLA)) are the molecules that help the B and T cells to distinguish between the normal and affected cells of the body (Chaplin 2010). The MHC molecules express a small component of the infective organism or the toxin or the tumor cell on the surface of the host cell, thereby prompting the immune cells to attack the affected cells of the body and kill them. Whenever there is a malfunction of this component of the immune system, it turns the B and T cells against the normal cells of the body leading to a wide variety of autoimmune diseases.

The immune system plays a major role both in disease progression and in treatment of various cancers. Progression of cancer in human body is attributed to failure of the immune system to check the process of multiplication of tumor cells from the initial stages. Treatment of cancer therefore, quite obviously, involves the use of certain medications which will activate the immune system of the body which will, in turn, mount a defense against the cancer cells and kill them. However, certain cancer chemotherapeutic agents also tend to suppress the immune system by destroying bone marrow which in turn blocks synthesis of various components of the immune system.

13.3 Anticancer Immune Surveillance

According to the immune surveillance theory, initiation and progress of any cancer eventually happen due to a failing immune system (Schreiber et al. 2011; Zitvogel et al. 2006). This makes boosting the immune system an important goal in treating cancers. The gradual increase in the use of specific agents that modulate the immune system, targeted agents, in cancer treatment has further strengthened the cause of reinstating a full-fledged immune system in a cancer patient. The baseline composition and function of various components of the immune system is a major prognostic marker in cancer patients (Fridman et al. 2012). However, studies in various animal models have also suggested immune system acts as a double-edged sword when it comes to cancer. Certain components of the immune system are protective, whereas there are few immunosuppressive components as well which prevent the killing of cancer cells. This immune surveillance is called immunoediting (Schreiber et al. 2011) and consists of three phases:

Elimination phase: Destruction of the cancer cells by the immune system.
Equilibrium phase: Production of cancer cells surpasses the destruction creating a pressure on the immune system. This also leads to genetic changes in the cancer cells (editing).
Escape phase: The edited cancer cells are resistant to the immune system and proliferate in the body leading to growth of the cancer.

The first two phases show an abundance of B and T cells in the cancer tissues, whereas in the third phase, there is a sudden paucity in numbers of these immune cells. This sudden shift shows the capability of cancer cells in not only generating their own immunosuppressive molecules but also attracting host immunosuppressive cells, thereby immobilizing the entire immune system.

13.4 Clinical Scenario for Use of Chemotherapeutic Agents

Drugs that have been used as conventional chemotherapeutic agents are those that destroy the tumor cells with or without any effect on the immune system. The reasons for use of chemotherapeutic agents may be treatment of blood cancers,

treatment in advanced cases once the cancer has spread to other organs (metastasis), and for reducing the size of the tumor before exposing it for surgery or radiotherapy.

Primary chemotherapy: It refers to the use of chemotherapeutic agents as the main modality of treatment when no other alternative exists. This is commonly used in case of blood cancers or advanced stages of any cancer when the aim of treatment is to prolong the life of the patient. It is primarily used in leukemia and lymphomas, and childhood tumors like Wilm's tumor.

Neoadjuvant chemotherapy: It refers to use of chemotherapeutic agents in those cancers where alternative therapy like surgery is the mainstay of treatment but is less efficacious when used singly ("How Is Chemotherapy Used to Treat Cancer?" 2016). Initially, cancer chemotherapy is administered for a short period which helps in reducing the bulk of the tumor. This is subsequently followed by surgery or radiotherapy. After the definitive procedure, chemotherapy is again continued for another 3–4 cycles for better control. Neoadjuvant chemotherapy has been found to be highly effective in cancers like bladder cancer, breast cancer, nonsmall cell type of lung cancer, and laryngeal cancer.

Adjuvant chemotherapy: The main aim of chemotherapy in this setting is to prevent the recurrence of the tumor and improve the overall survival of the patient ("How Is Chemotherapy Used to Treat Cancer?" 2016). Adjuvant chemotherapy is usually administered after surgical removal of the tumor or following radiotherapy. It has been used with great success in breast cancer, colon cancer, and gastric cancer among others.

13.5 Conventional Cancer Chemotherapeutic Agents

The logical goal in treating cancers is destruction of the tumor cells. This has been traditionally achieved by the use of cytotoxic agents which, as the name suggests, are toxic to the rapidly progressing cancer cells. Based on their principal mechanism of action, conventional cancer chemotherapy drugs can be broadly subdivided into (Galluzzi et al. 2015):

Alkylating agents: They contain an alkyl group that attaches to the DNA of the malignant cells and prevents the replication of the same (e.g., cyclophosphamide).

Platinum analogs: Platinum complex binds to the DNA of the tumor cells, thereby preventing the replication of these cells and subsequently leading to the death of the same (e.g., cisplatin).

Antimetabolites: They act by interfering with the DNA and RNA synthesis in the cells, thereby restricting the growth and multiplication of cancer cells (e.g., 5-fluorouracil [5-FU]).

Topoisomerase inhibitors: Topoisomerases are enzymes that help in separating the double-stranded structure of DNA before replication and then rejoining of the replicated strands of DNA to form the double strand again. Inhibition of these

enzymes leads to DNA damage, thereby causing death of the cancer cells (e.g., irinotecan).

Microtubular poisons: They bind to the cancer cells during mitosis or cell division and thereby prevent replication of the same (e.g., paclitaxel).

Cytotoxic antibiotics: They exert their action either by deranging DNA synthesis by preventing action of topoisomerase enzyme or by generating free radicals which further increase the killing of tumor cells (e.g., bleomycin).

Conventional chemotherapeutic agents, albeit predominantly kill the cancer cells, have been found to exert some action on the cells of the immune system as well. For example, taxane-based neoadjuvant therapy in breast cancer patients has been shown to increase the immune response in the body and thereby increase the overall survival of the patient (Issa-Nummer et al. 2013; Senovilla et al. 2012).

Increase in CD20 (a marker for showing B-cell activity) levels in biliary tract (Goeppert et al. 2013) and colorectal cancers (Kasajima et al. 2010), increase in CD4 (a marker for showing T-cell activity) levels in malignant melanoma (Mignot et al. 2014), increase in CD3 and CD8 (markers for showing T-cell activity) levels in ovarian cancer (Han et al. 2008), and increase in CD68 (a marker for showing macrophage activity) levels in gastric (Wang et al. 2011) and pancreatic cancers (Di Caro et al. 2016) have been associated with overall prolonged survival after cancer chemotherapy. High levels of B and T cells have been associated with poor prognosis as well. Increase in CD20 levels in malignant melanoma (Neagu et al. 2013), increase in CD68 levels in breast cancer (DeNardo et al. 2011), and increase in CD138 (a marker for plasma cell activity) levels in breast cancer (Mohammed et al. 2013) and malignant melanoma (Neagu et al. 2013) have been associated with low survival and bad prognosis.

13.6 Immunological Effects of Commonly Used Cancer Chemotherapeutic Drugs

Conventional anticancer drugs have been shown to help in mounting a robust immunological attack against cancer cells in both clinical and animal studies. The effects of these agents on immune system have been shown in Table 13.1.

However, not all anticancer agents produce a favorable immune response. Most of the anticancer drugs, when given at the highest dose that is safe, produce immunosuppression leading to destruction of bone marrow and reduced number of WBCs in the body. Sometimes, combination anticancer therapy has produced immune stimulatory responses. This might be attributed to the lower toxicity of the individual drug as the dose is reduced when given in a combination therapy with other anticancer agents.

Table 13.1 Immunological effects of conventional anticancer drugs

Drug	Effect on immune system
Bleomycin	Promotes immunological cell death of tumor cells and stimulates action of T helper cells (Bugaut et al. 2013)
Cyclophosphamide	Restores T-cell function (Gershan et al. 2015; Ghiringhelli et al. 2007) Increases macrophage function (Wu and Waxman 2015) Expands the production of stem cells in bone marrow (Ding et al. 2014)
Docetaxel	Favors immunosurveillance (Senovilla et al. 2012, Valent et al. 2013)
Doxorubicin	Promotes immunological cell death of tumor cells (Casares et al. 2005) Favors the expansion of stem cells in bone marrow (Ding et al. 2014)
5-FU	Increases infiltration of tumor cells by T lymphocytes (Lim et al. 2014) Increases expression of MHCs on cancer cells (Khallouf et al. 2012) Favors stem cell differentiation in bone marrow when given as a combination regimen in colorectal cancer (Kanterman et al. 2014)
Gemcitabine	Increases circulating monocytes (Soeda et al. 2009) Improves recruitment of natural killer cells (Liu et al. 2010; Xu et al. 2011) Enables action of targeted chemotherapeutic agents (Sawant et al. 2013)
Irinotecan	Increases stem cell production in the bone marrow when given as combination therapy in colorectal cancer (Kanterman et al. 2014)
Oxaliplatin	Promotes T-cell-dependent immune reaction to cancer cells (Shalapour et al. 2015) Promotes immunological death of cancer cells (Martins et al. 2011) Promotes activity of neutrophils and macrophages on cancer cells (Iida et al. 2013)
Paclitaxel	Promotes tumor infiltration by macrophages (DeNardo et al. 2011) Promotes tumor infiltration by T lymphocytes (Demaria et al. 2001)

13.6.1 Other Uses of Cancer Chemotherapeutic Agents

Considering the multitude effect of anticancer agents on the immune system, these drugs have been used in various other autoimmune disorders, wherein the immune system of the host produces antibodies against its own cells and destroys them. Rheumatoid arthritis is one such autoimmune condition where anticancer drugs have been used to halt the progression of the disease by inhibiting the action of the cells of the immune system on various joints. Cyclophosphamide, methotrexate, and thalidomide have been used routinely in the treatment of rheumatoid arthritis ("Chemotherapy Drugs Used to Treat Arthritis" 2016). Methotrexate has also been used in psoriasis, an autoimmune skin condition, with good results. Cyclophosphamide has been used in other autoimmune conditions like Wegener's granulomatosis and nephrotic syndrome. Thalidomide is one of the drug of choice in case of type I lepra reaction, an autoimmune complication seen in leprosy ("Thalidomide: Research advances in cancer and other conditions" 2016). Anticancer drugs have also been used as radiosensitizers. Radiosensitizers are agents that sensitize the tumor cells to radiation therapy, thereby maximizing the effects of radiation therapy in the treatment of various cancers (Raviraj et al. 2014). Anticancer agents that have been used as radiosensitizers include 5-FU, gemcitabine, fludarabine, paclitaxel, docetaxel, and irinotecan.

13.7 Toxicity of Conventional Anticancer Drugs on Immune System

Bone marrow suppression: This is one of the commonest side effects seen with antitumor agents. There is an overall reduction in the production of RBCs, WBCs, and platelets in the bone marrows. Bone marrow suppression manifests as anemia (reduction in the number of RBCs), increased susceptibility to infections (reduction in the number of WBCs), and increased bleeding tendencies (reduced number of platelets). This side effect does not manifest immediately because the already formed blood products (RBCs, WBCs, and platelets) have to be consumed first before the manifestations of bone marrow suppression are seen. WBCs are affected the most since they have a very short life span of 6–12 h and the reserves thus get used up very early. RBCs, with a life span of 120 days, are affected the least by bone marrow suppression. The full-blown effects of bone marrow suppression are normally evident by 10–14 days with most of the chemotherapeutic agents.

However, the onset is delayed with certain drugs like nitrosoureas and mitomycin (Medina and Fausel 2008). Onset of fever during the chemotherapy course is the commonest symptom suggestive of bone marrow suppression. The drugs might have to be temporarily stopped, or the dosage reduced till the blood counts come back to the normal range. However, in certain cases, reduction of the drug dosage might lead to bad prognosis of the disease. Hence, a judicious decision has to be taken. Blood transfusion used to be the most common treatment option for correcting anemia. However, the current treatment guidelines recommend the use of epoetin alfa or darbepoetin alfa, which are erythropoietic agents (increase the production of RBCs in the bone marrow). Iron supplementation is necessary for further optimizing RBC production. Since fever, which is a sign of infection, is the most common manifestation of reduction in the number of WBCs, treatment usually consists of antibiotics to resolve the underlying infection. However, in some cases, when the WBC number falls down to dangerously low levels, colony-stimulating factors (CSFs), which increase the production of WBCs in the bone marrow, can be used. Reduction in the number of platelets is managed by platelet transfusion to prevent any episode of bleeding.

Secondary malignancies: Drugs like alkylating agents, anthracyclines, and etoposide have been associated with causing this long-term serious complication. Blood cancer is the most common secondary malignancy seen in majority of cancer patients (Medina and Fausel 2008).

13.8 Targeted Cancer Chemotherapy

Conventional cancer chemotherapeutic agents acted as a double-edged sword. On the one hand, they killed the cancer cells in the body, whereas they also had a detrimental effect on the normal cells of the body. This led to the cascade of side effects seen with these drugs, immunosuppression, anemia, and bleeding episodes being the most common ones. As cancer research expanded, scientists came up with

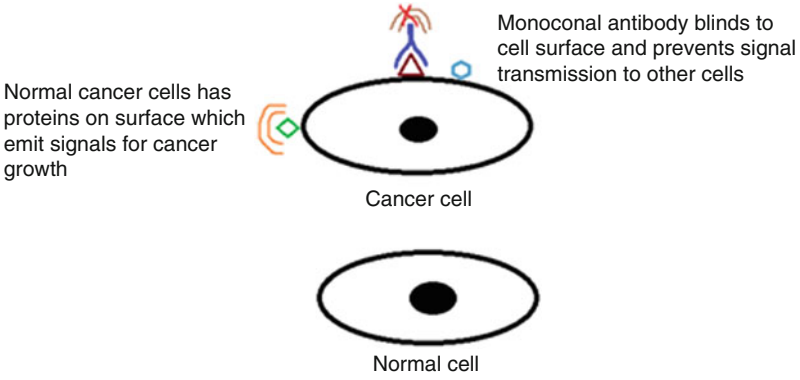

Fig. 13.2 Mechanism of action of monoclonal antibodies

more and more cellular features and metabolic pathways that were unique to the tumor cells. This helped in developing drugs which specifically targeted tumor cells only with minimal or no effect on the normal body cells. Targeted cancer chemotherapy is thus defined as a special type of cancer chemotherapy which takes advantage of the difference between cancerous cells and normal cells of the body ("What Is Targeted Cancer Therapy?" 2016). It is used along with other antitumor agents or as an adjunct to surgery or radiotherapy.

Cancer cells differ from the normal cells in certain perspectives:

They divide and multiply more rapidly than the normal cells of the body.

Certain genetic changes (mutations) help in converting a normal cell to a cancerous cell.

Tumor cells then generate certain signals that further aids in the rapid growth and multiplication of other cancerous cells.

As cancer cells are growing at a more than normal rate, their requirement for nutrients increases many folds. This is met by an increase in the blood vessels around the cancer cells which facilitate the provision of nutrients to the cancer cells.

Targeted cancer chemotherapeutic agents disrupt any of these processes, or they can trigger the natural defenses of the body to kill the cancerous cells. These targeted cancer chemotherapeutic agents are also known as monoclonal antibodies (Nelson et al. 2000). These drugs have features akin to the antibodies present naturally in the body. They have selective action against certain types of cancer cells or certain proteins which are expressed on the surface of cancer cells specifically. Monoclonal antibodies either kill the cancer cells directly or in most cases prevent generation of signals by cancer cells which is necessary for growth of cancer cells. This has been represented in Fig. 13.2.

Rituximab (a monoclonal antibody against CD20) was the first among these targeted therapies which was approved for use in cancer chemotherapy (Medina and Fausel 2008). It is a monoclonal antibody which activates the B cells, responsible for producing immunity in the body. Once these B cells are activated, they attack the tumor cells and kill them leading to reduction in tumor size. Tumors express a

wide range of growth factors which are important for the growth and multiplication of tumor cells, notable among them being epithelial growth factor and vascular endothelial growth factor. Drugs like cetuximab, trastuzumab, erlotinib, and gefitinib inhibit various epithelial growth factors and therefore block signaling pathways associated with growth and development of cancer cells. The development of new blood vessels around tumor cells is of paramount importance for delivery of nutrients to the cancer cells which in turn helps in the rapid multiplication of these cells. Vascular endothelial growth factors aid in new blood vessel formation, and drugs like bevacizumab, sunitinib, and sorafenib inhibit these factors. In chronic myeloid leukemia (CML), a variant of blood cancer, there is a specific mutation that leads to breakage in two chromosomes and the resealing of the broken parts (BCR-ABL mutation) leads to the formation of Philadelphia chromosome. Imatinib is a targeted chemotherapeutic agent that specifically blocks the action of this Philadelphia chromosome and thus prevents the spread of CML (Medina and Fausel 2008). Another group of drugs, bortezomib and carfilzomib, inhibit the protein synthesis inside the tumor cells. Since proteins are required for the normal functioning of all cells, inhibition of protein synthesis leads to death of cancer cells.

Targeted cancer chemotherapeutic agents have been used in a wide variety of cancers like leukemia, solid organ tumors like colorectal cancer, lung cancer, breast cancer, head and neck cancers, and pancreatic cancer (Medina and Fausel 2008). These agents have become the first-line therapy as part of a combination therapy in various kinds of cancers albeit high cost of the drug still remains a major concern.

Although targeted cancer chemotherapy heralded a new era in the treatment of cancers, they are not without their share of adverse effects. The most common side effect seen with these agents is hypersensitivity seen during injecting the drug into the body. Chances of allergic reactions are highest with the first dose of the drug. Hence, before starting intravenous injections of these chemotherapeutic agents, it is preferred to administer antiallergic medications like diphenhydramine to all the patients. The injection should be given at a very slow rate, and the patient should be observed thereafter for any signs of allergy like fever, rash, itching, swelling of eyes, and lips. Medications inhibiting vascular endothelial growth factors can increase the blood pressure. Diarrhea is a common side effect seen with drugs like imatinib (Medina and Fausel 2008).

13.9 Immunological Effects of Targeted Anticancer Agents

Monoclonal antibodies have more precise and accurate effects on the immune system as compared to the conventional anticancer agents. Effects of these targeted chemotherapeutic drugs have been demonstrated in combination therapies only. These have been briefly described in Table 13.2.

Table 13.2 Immunological effects of certain targeted anticancer drugs

Drug	Effect
Bevacizumab	Reduces T cells within the tumor, thereby preventing growth of the tumor (Terme et al. 2013)
Erlotinib	Increases susceptibility of cancer cells toward natural killer cells leading to increased cell death (Kim et al. 2011)
Gefitinib	Increases susceptibility of cancer cells toward natural killer cells leading to increased cell death (He et al. 2013; Kim et al. 2011)
Imatinib	Promotes circulation of natural killer cells that kill the cancer cells in CML (Mizoguchi et al. 2013) Promotes the production of BCR-ABL1-specific cytotoxic T lymphocytes in CML (Riva et al. 2014) Increases production of interferon γ that kills cancer cells (Ménard et al. 2009) Enhances destruction of cancer cells by antibodies (Murray et al. 2014)
Sorafenib	Increases accumulation of natural killer cells in the cancer tissues (Romero et al. 2014)
Sunitinib	Increases the cytotoxic T-cell levels in tumor tissues (Roselli et al. 2013)
Vorinostat	Increases levels of interferon-γ-producing T lymphocytes and promotes killing of cancer cells by plasma cells (West et al. 2013)

13.10 Conclusion

Conventional cancer therapy always has been directed at killing the tumor cells, and this in turn has caused notable adverse effects to the normal cells of the body as well. Traditionally cancer chemotherapy has always been associated with a decrease in the quality of life of the cancer patients due to the inadvertent immunological side effects associated with the use of these drugs. Targeted cancer chemotherapeutic drugs thus proved to be an invaluable weapon in the treatment of various types of cancers with clinically significant results. However, as more proof gathers regarding the modulation of the immune system by both conventional and targeted anticancer agents, treatment modalities in various cancers are bound to go through a major change.

As more evidence regarding the immune stimulatory role of conventional anticancer agents like methotrexate, cyclophosphamide, bleomycin, and cisplatin comes to light, the combination of these agents with immune modulatory drugs seems a much safer and more effective treatment plan. Combination can either be based on the principle of: (a) counteracting the immunosuppressant action of anticancer drugs by targeted agents or (b) boosting the immune stimulatory action of conventional anticancer agents.

Overall survival in cancer has tremendously increased due to the emergence of various new treatment modalities. The development of the concept of modulating the immune system to control the growth rate of tumors instead of directly killing the cancer cells has thus paved the way for use of both the conventional and newer cancer chemotherapeutic agents as combination therapies. The optimal use of these combination therapies, their long-term benefits, and adverse effects on cancer patients, however, are few of the important questions that still remain unanswered.

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