A LITERARY EXPLORATION OF CANCER TREATMENT TECHNOLOGIES

Shruti M. Thakre*, Prashant L. Takdhat and Gauri A. Nilewar

Dr. R. G. Bhoyar Institute of Pharmacy, Wardha - 442001 Maharashtra, India.

ABSTRACT
Cancer is a group of disorder characterized by uncontrolled and abnormal cellular growth. There are more than 100 different types of cancer. The WHO projects that the number of new cancer diagnoses will reach 22 million per year in the next two decades. Cancer is one of the world’s most pressing health care challenges. Extensive research and study every year brings new knowledge and insights that help further research and ultimately improve the outlook for the patients with cancer. Despite advancement in treatment technology, there is no ideal treatment till date. Cancer immunotherapy is now a standard treatment option for people with a growing number of different cancers. Immune related adverse events, atypical clinical response patterns, durable responses, a chance to live longer and event free survival benefit distinguish cancer immunotherapy from cytotoxic cancer therapy. The clinical trial study explores whether combining immunotherapy treatments with one another or with other cancer treatments, such as radiation therapy and chemotherapy, might extend the impact of this new group of therapies. These recent years marked many milestones in the cancer treatment such as immune checkpoint blockers and chimeric antigen receptor (CAR) T-cell therapy. In addition to the rapidly evolving immunotherapy, recent years also brought the advances in targeted therapy and chemotherapy. This article encompasses the traditional cancer therapies along with newly emerging cancer therapies and drugs approved in these therapies.

KEYWORDS: Surgery, radiation therapy, chemotherapy, immunotherapy, CAR-T cell.

INTRODUCTION
Cancer is considered to one leading cause of mortality and morbidity worldwide. On World Cancer Day 4 February, WHO highlights the tremendous toll of cancer and accounts for
almost one in six deaths globally. It also highlights that cancer no longer needs to be a death sentence, as the capacity exists to reduce its burden and improve the survival and quality of life of people living with disease. New WHO figures indicate that cancer deaths continue to increase.

Cancer is a class of disease characterized by uncontrolled cell growth.[2] This can happen when the cell’s instructions (DNA) are damaged, which can result in a mutation. A mutation is a change in the cell structure.[3][4] If cells keep reproducing in an uncontrolled way, a mass forms. This solid mass of cells is called a growth or a tumor. Tumors can be benign and malignant.[2] **Benign tumors** are not cancer, do not spread to other parts of the body and are not usually a threat to someone’s life. **Malignant tumors** are cancer cells which reproduce without control or order. Cancer cells can spread to other parts of the body.[5][6][7]

Metastasis and the invasion of normal tissue by cancer cells are the hallmarks of malignancy. Metastasis is the general term used to describe the spread of cancer cells from the primary tumor to surrounding tissues and to distant organs.[2] Metastasis involves a series of sequential and interrelated steps. In order to complete the metastatic cascade, cancer cells must detach from the primary tumor, intravasate into the circulatory and lymphatic systems, evade immune attack, extravasate at distant capillary beds, and invade and proliferate in distant organs.[8][9][10]

Angiogenesis, the recruitment of new blood vessels, is an essential component of the metastatic pathway. These vessels provide the principal route by which tumor cells exit the primary tumor site and enter the circulation. For many tumors, the vascular density can provide a prognostic indicator of metastatic potential, with the highly vascular primary tumors having a higher incidence of metastasis than poorly vascular tumors.[11][12]

**Management of cancer:** Once cancer is diagnosed, the patient may require medical treatment and specialized care for months and often years. The principle modes of therapies are surgery, chemotherapy, radiation, hormonal, and targeted therapy (including immunotherapy such as monoclonal antibody therapy and gene therapy), precision medicine. The choice of therapy depends upon the location and grade of the tumor and the stage of the disease, as well as the general state of the patient.[13][14]
The aim of treatment for cancer may be: cure, control and prolongation of life and improve the quality of remaining life after the diagnosis of cancer is confirmed by the appropriate available procedures. Patients can benefit either by cure or by prolonged life, in cases of cancers that although disseminated are highly responsive to treatment, including acute leukemia and lymphoma. Palliative care meets the needs of all patients requiring relief from symptoms, and the needs of patients and their families for psychosocial and supportive care. This is particularly true when patients are in advanced stages and have a very low chance of being cured, or when they are facing the terminal phase of the disease. Because of the emotional, spiritual, social and economic consequences of cancer and its management, palliative care services addressing the needs of patients and their families, from the time of diagnosis, can improve quality of life and the ability to cope effectively.\[15\]

1. **Surgery**: Surgery is the primary method of treatment for most isolated, solid cancers and may play a role in palliation and prolongation of survival. In theory, some cancers can be cured if entirely removed by surgery, when these cancers are likely to occur in non-essential organs, the potentially involved organ may be removed or the anatomical, developmental or genetic defect corrected to prevent or reduce risk of subsequent malignancy. When the cancer has metastasized to other sites in the body prior to surgery, complete surgical excision is usually impossible. Surgery can be a simple, safe method to cure individuals with solid tumors when the tumor is confined to the anatomic site of origin. Resection of the primary cancer involves definitive surgical treatment encompassing a sufficient margin of normal tissue to achieve a cure with surgery alone.\[16\][17]

Examples of surgical procedures for cancer include mastectomy for breast cancer, prostatectomy for prostate cancer, and lung cancer surgery for non-small cell lung cancer. Surgery may be performed before or after other forms of treatment. Treatment before surgery is often described as neoadjuvant.\[18\] In breast cancer, the survival rate of patients who receive neoadjuvant chemotherapy is no different to those who are treated following surgery.\[19\]

2. **Radiation Therapy**: Radiation therapy is based on the fact that ionizing radiations (x-rays, γ rays, and charged particles) are able to penetrate the tissue death, destroying tumor cells even from deep layers.\[20\] Radiotherapy can be used alone, or as an effective neoadjuvant and adjuvant treatment in combination with other treatment modalities such as surgery, antineoplastic agents and hormonal therapy.\[21-24\] The aim of radiotherapy may be cure,
control, or palliation to offer benefits in terms of organ preservation, quality of life, survival outcomes and effective alleviation of symptoms.\cite{25,26}

Radiation therapy can be administered externally via external beam radiotherapy (EBRT) or internally via brachytherapy, combined modality treatment. This enables a range of radiotherapy schedules that best suit the tumor type and stage of a cancer to be considered.\cite{23,27} Radiotherapy aims to treat cancer through delivering sufficient doses of ionizing radiation to a specific area of the body to damage target DNA that eventually results in cell death.\cite{28} Ionizing radiation causes cell death (either directly or indirectly). Direct damage to the atoms that make up the DNA results in either single or double-strand breaks, faulty cross-linking of chains after breakage, damage or loss of a nitrogenous base, or breakage of the hydrogen bond between the two chains of the DNA molecule causing impaired cellular functioning or cell death.\cite{21} Indirect damage is caused by the interaction of ionizing radiation with the molecules of the cellular fluid, resulting in toxic changes due to the creation of unstable free radical ions that impair cellular functioning.\cite{29}

Radiation therapy may be used to treat almost every type of solid tumor, including cancers of the brain, breast, cervix, larynx, liver, lung, pancreas, prostate, skin, stomach, uterus, or soft tissue sarcomas. Radiation is also used to treat leukemia and lymphoma.\cite{30} Although radiation damages both cancer cells and normal cells, most normal cells can recover from the effects of radiation and function properly. Normal body tissues vary in their response to radiation. As with tumors, normal tissues in which cells are quickly dividing may be affected. This causes some of the side effects of radiation treatment. Since radiation is a local treatment, side effects depend on the area of the body being treated. The early effects of radiation may be seen a few days or weeks after treatments have started and may go on for several weeks after treatments have ended. The most common side effects are skin problems, fatigue, head and neck-dry mouth, mouth and gum source, tooth decay, shortens of breath, cough, fever, Nausea, vomiting, diarrhea, infertility.\cite{31,32}

3. **Chemotherapy:** The process of anticancer drugs used to kill cancer cells is known as chemotherapy. After or before surgery chemotherapy can be used without using radiation therapy.\cite{33} Antineoplastic agents frequently disrupt replication at the cellular level by obstructing the synthesis of new genetic material or by causing irreversible damage to the DNA itself. While this affects both normal and malignant cells, normal cells have a greater ability to repair minor damage and continue living. The increased weakness of malignant
cells is exploited to achieve the therapeutic effects seen with the administration of antineoplastic agents.\textsuperscript{[34]} The mechanisms of action of antineoplastic agents are based on the concepts of cellular kinetics – cell cycle time, growth fraction, and tumour burden.\textsuperscript{[35]} In the broad sense, most chemotherapeutic drugs work by impairing mitosis (cell division), effectively targeting fast-dividing cells. They prevent mitosis by various mechanisms including damaging DNA and inhibition of the cellular machinery involved in cell division.\textsuperscript{[36]} Chemotherapy is a modality that is predominantly used in the treatment of cancer disease, with metastases and dissemination. Depending on the primary location and the extension of the disease, chemotherapy can be curative or palliative. In the majority of cases, chemotherapy leads to the prolongation of survival, and in other cases it results in the eradication of the disease. Chemotherapy can be in most cases a major adjuvant to surgical therapy and/or radiotherapy.

Drugs have been classified according to their preferential destruction effect in the cell cycle, based on kinetic cell culture studies. The different classes of antineoplastic drugs are Alkylating and alkylating-like agents, Antimetabolites, Antitumour antibiotics, Plant alkaloids, Topoisomerase inhibitors, Miscellaneous agents, Hormonal agents.\textsuperscript{[34][37][38]}

The role of antineoplastic agents in cancer control includes:\textsuperscript{[39][40]}

- **Induction Chemotherapy**: It is the initial therapy administered with the aim of achieving significant cytoreduction, and ideally, completes remission of disease.

- **Consolidation / intensification Chemotherapy**: It is administered following induction to prolong freedom from disease and overall survival. While consolidation therapy uses the same agents as induction therapy, intensification therapy uses agents which are non-cross resistant to induction therapy.

- **Adjuvant treatment**: It is used in conjunction with another treatment modality i.e. biotherapy, radiotherapy or surgery, and aimed at treating micro-metastases and preventing local recurrence.

- **Neo-adjuvant treatment**: It is designed to reduce the size of a tumor before definitive treatment.

- **Maintenance therapy**: It is prolonged, low-dose therapy administered to extend the duration of remission and achieve cure.

- **Combination therapy**: It involves the use of two or more agents to treat the disease.
• **Salvage therapy**: It is given after failure of other treatments to control disease or provide palliation.

3.1. **Adverse effect of chemotherapy**: Chemotherapy-induced adverse effects are most commonly caused by damage of rapidly dividing normal cells, such as bone marrow cells, cells lining the gastrointestinal and reproductive tracts, as well as cells of hair follicles. Most chemotherapy drugs affect all these types of cells, but to varying degrees depending on the drug, dose, and route of administration and patient characteristics. Genetic variants of liver enzymes involved in drug metabolism probably account for some of the observed inter-individual differences of adverse effects, but have yet to reach clinical application. The most common adverse effects includes hypersensitivity reactions, bone marrow depression – neutropenia, thrombocytopenia, nausea, vomiting, anorexia, diarrhea and constipation, anemia, fatigue, alopecia, peripheral neuropathy, sexual dysfunction, reproduction, and pregnancy, cardiotoxicity, hepatotoxicity, nephrotoxicity, ototoxicity, etc.\(^1\)\(^2\)

3.2. **Resistance to Cancer Chemotherapy**: While many anticancer drugs, either alone or in combination, dramatically affect the course of malignant disease, success is far from universal. Certain tumor types are relatively refractory to anticancer drugs. In other instances, a marked response to treatment occurs but, over time, the disease process recurs and drugs, both those originally used and agents not previously employed, are ineffective. This phenomenon is referred to as drug resistance. Typically, resistance is attributable to mutation or altered expression of genes whose products mediate the transport of a drug(s) into or out of the cell, the metabolism and hence the intracellular concentration of the drug, and the structural or enzymatic protein to which the drug binds to cause cytotoxicity.\(^3\)

3.3. **Advances in Chemotherapy**: Even in the era of precision medicine, chemotherapy remains a key treatment modality for many patients with cancer. The past year brought important advances in chemotherapy for treatment of patients with pancreatic cancer and leukemia (Table 1).
Table 1: Notable Food and Drug Administration (FDA) approvals of Cancer Chemotherapy.

<table>
<thead>
<tr>
<th>Cancer type</th>
<th>Drug (Trade name)</th>
<th>Key Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreatic Cancer</td>
<td>Capecitabine and Gemcitabine</td>
<td>Adding capecitabine, to gemcitabine can help such patients live even longer, despite a small difference in median survival, addition of capecitabine increased the chance of surviving 5 years from 16% to 29%.[44]</td>
</tr>
<tr>
<td>Therapy-related Acute Myeloid Leukemia (t-AML)</td>
<td>Daunorubicin and Cytarabine (Vyxeos)</td>
<td>The recently approved (Aug 2017) Vyxeos estimated longer median overall survival than standard combination of same drugs (9.6 vs 5.9 months respectively).[45]</td>
</tr>
</tbody>
</table>

4. Targeted Therapy: In most solid tumors, after its surgical removal, the remaining cancer cells are managed with a variety of treatment options including, radiotherapy, chemotherapy, immunotherapy, etc.[46] However, once the cancer is metastasized, the treatment options are limited, and chemotherapy remains the choice of treatment. The main reason for failure of chemotherapy is the poor accessibility of antineoplastic agents to the tumor, requiring higher doses, and the nonselective nature of these agents causes severe toxicity.[47] Thus, targeted drug delivery holds immense potential to improve the treatment of cancer by selectively providing therapeutically effective drug concentrations at the tumor site. A primary goal of targeted therapy is to fight cancer cells with more precision and potentially fewer side effects. For this reason it is a promising therapy for the 3rd millennium.[48] Currently, molecularly targeted therapies utilize either monoclonal antibodies or small molecular weight (SMW) tyrosine kinase inhibitors (TKIs).

4.1 Monoclonal Antibodies: Monoclonal antibody therapy is another strategy in which the therapeutic agent is an antibody which specifically binds to a protein on the surface of the cancer cells. In some cases, monoclonal antibodies are conjugated to radio-isotopes or toxins to allow specific delivery of these cytotoxic agents to the intended cancer cell target. Examples include the anti-HER2/neu antibody trastuzumab (Herceptin) used in breast cancer, and the anti-CD20 antibody rituximab, used in a variety of B-cell malignancies.[49][50]

4.2 Small molecules: Small molecule targeted therapy drugs are generally inhibitors of enzymatic domains on mutated, over expressed or otherwise critical proteins within the cancer cell.[51] Prominent examples are the tyrosine kinase inhibitors imatinib.[52-54]
Thakre et al. World Journal of Pharmaceutical Research

(Gleevec/Glivec) and gefitinib (Iressa). Another common example is the class of Bcr-Abl inhibitors, which are used to treat Chronic Myelogenous Leukemia (CML).\[^{[52]}\]

These drugs are now a component of therapy for many common cancers, including breast, colorectal, lung and pancreatic, lymphoma, leukemia and multiple myeloma. The mechanisms of action and toxicities of targeted therapies differ from those of traditional chemotherapy. Targeted therapies are generally better tolerated than traditional chemotherapy, but they are associated with several toxicities, such as acniform rash, cardiac dysfunction, thrombosis, hypertension and proteinuria, or resistance because acquired mutations on target molecules.\[^{[51][55][56]}\]

### 4.3 Advances in Targeted Therapy:

In addition to the growing success seen with immunotherapy, past few years were marked by a wave of advances in treatments directed at novel molecular targets (Table 2).

**Table 2: Notable FDA approvals of Targeted Therapy.**

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Drug (Trade name)</th>
<th>Key Findings</th>
<th>Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced (stage IIIB/C or IV)</td>
<td>Nivolumab (Opdivo)</td>
<td>Adjuvant therapy with nivolumab resulted in longer recurrence-free survival (RFS) (70% v 61% respectively) and a lower rate of grade 3 or 4 adverse events than adjuvant therapy with ipilimumab (14% v 46% respectively).[^{[92]}]</td>
<td>20-Dec-17</td>
</tr>
<tr>
<td>Melanoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-small cell lung cancer (NSCLC)</td>
<td>Atezolizumab (Tecentriq)</td>
<td>Compared with docetaxel, treatment with atezolizumab in the intended patient population in the two trials resulted in a 4.2 and a 2.9 months improvement in overall survival (OS), respectively.</td>
<td>18-Oct-16</td>
</tr>
<tr>
<td></td>
<td>Pembrolizumab (Keytruda.)</td>
<td>In combination with pemetrexed and carboplatin(PC) pembrolizumab demonstrated an improvement in ORR (55% vs 29% respectively) and PFS (13 months vs 8.9 months respectively) compared to PC alone.</td>
<td>10-May-17</td>
</tr>
<tr>
<td></td>
<td>Durvalumab (Imfinzi)</td>
<td>The trial demonstrated a statistically significant improvement in median PFS for durvalumab compared to placebo(16.8 months vs 5.6 months).</td>
<td>16-Feb-18</td>
</tr>
<tr>
<td>Cancer Type</td>
<td>Treatment</td>
<td>Description</td>
<td>Date</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>---------------------</td>
<td>-----------------------------------------------------------------------------</td>
<td>------------</td>
</tr>
<tr>
<td>Hodgkin’s Lymphoma</td>
<td>Nivolumab (Opdive)</td>
<td>Nivolumab produced a 65% ORR, with 58% partial remission, 7% complete remission and 8.7 months median duration of response.</td>
<td>17-May-16</td>
</tr>
<tr>
<td></td>
<td>Pembrolizumab (Keytruda)</td>
<td>With a median follow up of 9.4 months, the ORR was 69% and median response duration was 11.1 months.</td>
<td>14-Mar-17</td>
</tr>
<tr>
<td>Hepatocellular Cancer (HCC)</td>
<td>Nivolumab (Opdive)</td>
<td>In Sorafenib intolerant patients, responses to nivolumab were durable with encouraging ORR (14.3%), with 3 complete responses and 19 partial responses.</td>
<td>22-Sep-17</td>
</tr>
<tr>
<td>HER2-positive Breast cancer</td>
<td>Pertuzumab (Perjeta)</td>
<td>Addition of Pertuzumab to trastuzumab and adjuvant chemotherapy, at 3 years, an estimated 94.1% of patients in the pertuzumab group were free of invasive breast cancer compared with 93.2% of patients in the placebo group.</td>
<td>20-Dec-17</td>
</tr>
<tr>
<td>Merkel cell carcinoma</td>
<td>Avelumab (Bavencio)</td>
<td>Avelumab had an ORR of 33%, with 11% complete and 22% partial responses.</td>
<td>23-Mar-17</td>
</tr>
</tbody>
</table>

5. Immunotherapy: Cancer immunotherapy refers to a diverse set of therapeutic strategies designed to induce the patient’s own immune system to fight the tumor.\(^{[66]}\) Cancer immunotherapy involves the use of therapeutic modalities that lead to a manipulation of the immune system by using immune agents such as cytokines, vaccines, cell therapies, and transfection agents.\(^{[67]}\)

The Immune System and Cancer

The host immune system has a natural response to cancer, recognizing and eliminating abnormal cells with replicative errors, precancerous cells, and malignant tumor cells from the body. However, the equilibrium between tumor cells and the immune system can shift in favor of the tumor and can result in uncontrolled malignant growth. This escape process can involve the emergence of tumor cells with lower immunogenicity, which dampens the antitumor immune response below the threshold required for complete tumor elimination.\(^{[68]}\)

The immune response to tumor cells involves both the adaptive and innate components of the immune system. Adaptive antitumor immune responses are mediated by cellular and humoral components, with cytotoxic T lymphocytes (CD41 and CD81 T cells) having a key role. Natural killer (NK) cells have an important role in the innate antitumor immune response.\(^{[69–71]}\) Tumor cells exploit multiple complex mechanisms to escape recognition and destruction by the immune system. Immunotherapy of cancer stimulates the host’s anti-tumor response by
increasing the effector cell numbers (like DC based vaccines) and production of soluble mediators (like increased tumor cell immunogenicity) and decreases the host’s suppressor mechanisms by inducing tumor killing environment and by modulating immune checkpoints.\textsuperscript{[72]}

**Fig. 1: How Does Immunotherapy Work?**

Immunotherapy can trigger the immune system to fight cancer in different ways.

### 5.1 Monoclonal Antibodies (mAbs)

Monoclonal antibodies are molecules generated in the laboratory that can target specific antigens on tumors.\textsuperscript{[78]} Monoclonal antibody has very specific action and showing rare kind of toxicity. For the preparation of mAbs first thing is to identify the nature of antigen on the surface of cancer cells. After proper decoding the nature of antigen of many types, the scientists develop mAb and proving its efficacy against other kind of therapy of cancer. Antibody may target cancer indirectly by blocking the synthesis pathway of certain protein that is responsible for growth of tumor. As result of this action, cancer cell may die or stop further growth. Different mAbs work in different ways.

- **Naked monoclonal antibodies**: Naked mAbs are antibodies that work by themselves, no drug or radioactive material attached to them. Most naked mAbs attach to antigens on cancer cells, but some work by binding to antigens on other non-cancerous cells, or even free-floating proteins.
- **Conjugated monoclonal antibodies**: Monoclonal antibodies joined to a chemotherapy drug (Chemolabeled antibodies) or to a radioactive particle (Radiolabeled antibodies) are
called conjugated monoclonal antibodies. These mAbs are used as a homing device to take one of these substances directly to the cancer cells. These mAb circulate throughout the body until it can find and hook onto the target antigen. It then delivers the toxic substance where it is needed most. This lessens the damage to normal cells in other parts of the body.

- **Bispecific monoclonal antibodies**: These are designed to bind to two different proteins at once. Some attach to both a cancer cell and an immune system cell, helping promote immune attacks on the cancer. \[^{73}\]

### 5.2 Checkpoint inhibitors

Immune checkpoints are specialized proteins that act as brakes on the immune system, ensuring that immune defenses are engaged only when they are needed and for as long as they are needed. They prevent the immune system from becoming overactive, which can lead to excessive inflammation or autoimmune disease. Cancer treatments known as immune checkpoint inhibitors unleash the immune system to attack cancer. Since the first remarkable reports of immune checkpoint inhibitors shrinking advanced melanoma in 2011. \[^{74}\]

In the immune system, white blood cells have proteins on the surface of the cells that stop immune cells from attacking healthy cells. \[^{75}\][\(^{76}\]

**Fig. 2**: Mechanism of Immunocheckpoint Inhibitor.

- **Cytotoxic T- Lymphocyte Antigen (CTLA-4) inhibitors**: CLTA4 is a glycoprotein present in the intracellular compartment of CTLs. \[^{77}\] This protein interacts with a
corresponding protein that is expressed on cancer cells, and causes T cells to stop working. This prevents cancer cells from being destroyed by the T cells. CTLA4 was first discovered in the late 1980’s. Antibodies are Y-shaped molecules with ends that are like locks, which recognize specific structures, or keys. Antibodies against CTLA4 can be used to prevent CTLA4 from being turned on, allowing the immune cells to do their jobs.

- **PD-1 or PD-L1 inhibitors**: They target checkpoints called PD-1 or PD-L1 that are found on T cells in your immune system. PD-1 binds to its ligands, PDL-1 (B7-H1 or CD274)\(^{[78]}\) or PDL-2 (B7-H2 or CD273).\(^{[79]}\) While PDL-1 is ubiquitously expressed on the surface of activated T cells, B cells, dendritic cells or macrophages and some non-immune cells, PDL-2 expression is limited to activated macrophages and dendritic cells. The binding of PD-1 on activated T cells by PDL-1 or PDL-2 results in the recruitment of phosphatases to the immune synapse which dephosphorylate the molecules involved in TCR signaling, thus abrogating the immune signaling cascade.\(^{[80]}\) The examples of recently approved PD1 blockers are Nivolumab and Pembrolizumab, while PD-L1 blockers are Atezolizumab, Durvalumab and Avelumab.

### 5.3 Cancer vaccines

Cancer vaccines are designed to elicit an immune response against tumor-specific or tumor-associated antigens and are tried in esophageal cancer.\(^{[67]}\) Some strains of the Human Papilloma Virus (HPV) have been linked to cervical, anal, throat, and some other cancers. Vaccines against HPV may help protect against some of these cancers. People who have chronic (long-term) infections with the hepatitis B virus (HBV) are at higher risk for liver cancer. Some cancer treatment vaccines are made up of cancer cells, parts of cells, or pure antigens. Sometimes a patient’s own immune cells are removed and exposed to these substances in the lab to create the vaccine.

Sipuleucel-T (Provenge\(^{®}\)) - This is the only vaccine approved in the US to treat cancer so far. It’s used to treat advanced prostate cancer that is no longer being helped by hormone therapy.\(^{[81]}\)[82]

**Advances in Immunotherapy**: Research in the development of immune checkpoints and monoclonal antibodies has taken off at an incredible pace. Over the past year, the FDA approved many new uses for immune checkpoint inhibitors in many different types of cancers (Table 3).
Table 3: FDA Approved significant Recent Advances with Immunocheckpoint Inhibitors.

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Drug (Trade name)</th>
<th>Key Findings</th>
<th>Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced (stage IIIB/C or IV) Melanoma</td>
<td>Nivolumab (Opdivo)</td>
<td>Adjuvant therapy with nivolumab resulted in longer recurrence-free survival (RFS) (70% v 61% respectively) and a lower rate of grade 3 or 4 adverse events than adjuvant therapy with ipilimumab (14% v 46% respectively).[92]</td>
<td>20-Dec-17</td>
</tr>
<tr>
<td>Non-small cell lung cancer (NSCLC)</td>
<td>Atezolizumab (Tecentriq)</td>
<td>Compared with docetaxel, treatment with atezolizumab in the intended patient population in the two trials resulted in a 4.2 and a 2.9 months improvement in overall survival (OS), respectively.</td>
<td>18-Oct-16</td>
</tr>
<tr>
<td></td>
<td>Pembrolizumab (Keytruda.)</td>
<td>In combination with pemetrexed and carboplatin(PC) pembrolizumab demonstrated an improvement in ORR (55% vs 29% respectively) and PFS (13 months vs 8.9 months respectively) compared to PC alone.</td>
<td>10-May-17</td>
</tr>
<tr>
<td></td>
<td>Durvalumab (Imfinzi)</td>
<td>The trial demonstrated a statistically significant improvement in median PFS for durvalumab compared to placebo (16.8 months vs 5.6 months).</td>
<td>16-Feb-18</td>
</tr>
<tr>
<td>Hodgkin’s Lymphoma</td>
<td>Nivolumab (Opdivo)</td>
<td>Nivolumab produced a 65% ORR, with 58% partial remission, 7% complete remission and 8.7 months median duration of response.</td>
<td>17-May-16</td>
</tr>
<tr>
<td></td>
<td>Pembrolizumab (Keytruda)</td>
<td>With a median follow up of 9.4 months, the ORR was 69% and median response duration was 11.1 months.</td>
<td>14-Mar-17</td>
</tr>
<tr>
<td>Hepatocellular Cancer (HCC)</td>
<td>Nivolumab (Opdivo)</td>
<td>In Sorafenib intolerant patients, responses to nivolumab were durable with encouraging ORR (14.3%), with 3 complete responses and 19 partial responses.</td>
<td>22-Sep-17</td>
</tr>
<tr>
<td>HER2-positive Breast cancer</td>
<td>Pertuzumab (Perjeta)</td>
<td>Addition of Pertuzumab to trastuzumab and adjuvant chemotherapy, at 3 years, an estimated 94.1% of patients in the pertuzumab group were free of invasive breast cancer compared with 93.2% of patients in the placebo group.</td>
<td>20-Dec-17</td>
</tr>
<tr>
<td>Merkel cell carcinoma</td>
<td>Avelumab (Bavencio)</td>
<td>Avelumab had an ORR of 33%, with 11% complete and 22% partial responses.</td>
<td>23-Mar-17</td>
</tr>
</tbody>
</table>
Changing treatment paradigm with immunotherapy for bladder cancer: The most common type of bladder cancer, urothelial cancer, is difficult to treat at advanced stages. After 30 years of limited progress, the outlook for these patients is now improving with the arrival of a series of immunotherapies (Table 4). These immunotherapies are mostly approved for treatment of patients with locally advanced or metastatic urothelial carcinoma who experience disease progression during or after platinum-containing chemotherapy or who experience disease progression within 12 months of neoadjuvant or adjuvant treatment with a platinum containing chemotherapy.

Table 4: Remarkable FDA Approved Immunotherapies of Bladder Cancer.

<table>
<thead>
<tr>
<th>Drug (Trade name)</th>
<th>Key Findings</th>
<th>Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atezolizumab (Tecentriq)</td>
<td>The response rate to atezolizumab was 14.8% among all patients in the study and 26% in the group of patients with more PD-L1–positive immune cells.</td>
<td>18-May-16</td>
</tr>
<tr>
<td>Nivolumab (Opdivo)</td>
<td>Objective response rate with Nivolumab was 11%, with complete responses and partial responses</td>
<td>02-Feb-17</td>
</tr>
<tr>
<td>Durvalumab (Imfinzi)</td>
<td>Imfinzi had an objective response rate of 17% regardless of PD-L1 status and 26.3% in patients with high expression of PD-L1.</td>
<td>01-May-17</td>
</tr>
<tr>
<td>Avelumab (Bavencio)</td>
<td>Avelumab had an ORR of 13.3% in 30 patients for at least 13 weeks, and 16.1% in those for at least 6 months.</td>
<td>09-May-17</td>
</tr>
<tr>
<td>Pembrolizumab (Keytruda)</td>
<td>Pembrolizumab demonstrated significant improvements in overall survival (10.3 vs 7.4 months respectively) and ORR (21% vs 11% respectively) compared with chemotherapy alone</td>
<td>18-May-17</td>
</tr>
</tbody>
</table>

5.4 Adoptive Cell Transfer (CARs, TCRs, and TILs): Adoptive cell therapy (ACT) has multiple advantages compared with other forms of cancer immunotherapy that rely on the active in vivo development of sufficient numbers of antitumor T cells with the functions necessary to mediate cancer regression. For use in ACT, large numbers of antitumor lymphocytes (up to \(10^{11}\)) can be readily grown in vitro and selected for high-avidity recognition of the tumor, as well as for the effector functions required to mediate cancer regression. In vitro activation allows such cells to be released from the inhibitory factors that exist in vivo. ACT enables the manipulation of the host before cell transfer to provide a favorable microenvironment that better supports antitumor immunity. ACT is a “living” treatment because the administered cells can proliferate in vivo and maintain their antitumor effector functions.[83]
TIL Therapy: The first form of ACT to be tested in humans used immune cells collected from a patient’s tumor, called tumor-infiltrating lymphocytes (TILs). TILs are immune cells that have naturally entered a tumor, and their presence is thought to indicate that the immune system is trying to attack the cancer. The resected melanoma specimen is digested into a single-cell suspension or divided into multiple tumor fragments that are individually grown in IL-2. Lymphocytes overgrow, destroy tumors within 2 to 3 weeks, and give rise to pure cultures of lymphocytes that can be tested for reactivity against tumors, if available, in co-culture assays. Individual cultures are then rapidly expanded in the presence of excess irradiated feeder lymphocytes, an antibody targeting the epsilon subunit within the human CD3 complex of the TCR, and IL-2. By 5 to 6 weeks after resecting the tumor, up to $10^{11}$ lymphocytes can be obtained for infusion into patients.\[95] Indeed, the efficacy of naturally occurring TILs seems to be primarily restricted to melanoma, for reasons that are not fully understood.\[84]

TCR (T Cell Receptor) Therapy: TCRs are composed of one α chain and one β chain, and they recognize antigens that have been processed and presented by one of the patient’s own MHC molecules.\[84] The first report of tumor regression after administration of autologous TCRs described the treatment of metastatic melanoma with a TCR with specificity for MART1.\[85] Since then, other trials have tested TCRs against other antigens, including gp100 in melanoma\[86], carcinoembryonic antigen (CEA) in colorectal cancer\[87], and NY-ESO-1\[88] and MAGE-A3\[89] in melanoma and synovial sarcoma. Clinical responses were observed across trials. Some of the advantages of TCR T cells arise from the fact that these cells can be produced from peripheral blood T cells (unlike TILs) and can "see" intracellular antigens (unlike CARs).\[84]

CAR (Chimeric Antigen Receptor) T-Cell Therapy: The use of TCR T cells is limited by the fact that this therapy can only be proposed to MHC-compatible patients. In addition, tumors frequently lose antigen expression through down regulation of MHC. To overcome these limitations, CAR technology has been developed. CAR T cells are constructed by fusing an antibody-derived single-chain variable fragment (scFv) to T-cell intracellular signaling domains. Such T cells recognize cell surface antigens in a non–MHC-restricted manner. They do not depend on antigen processing and presentation. The first-generation CARs consisted of a scFv linked to the intracellular signaling domain of CD3x. To improve persistence and proliferation of infused T cells, second- and third-generation CARs were
developed that incorporate the intracellular domains of one or multiple costimulatory molecules, such as CD28, OX40, and 4-1BB (which reproduce the "second signal") within the endodomain. When targeted to tumor surface antigens, CAR T cells proliferate and kill tumor cells upon antigen contact. In CAR T cell therapy, T cells are isolated from blood of the patient or a donor, activated, and then genetically engineered to express the CAR construct. After ex vivo expansion of the CAR T cells, they are formulated into the final product. Similar to TCRs, CARs can be produced from peripheral blood T cells. The patient undergoes either a conditional chemotherapy or the CAR T cell product is directly infused.\[90\]

**Other immunotherapies:** The cytokines are group of protein with structurally diverse molecules and almost all concerned with immune response. Cytokines are involved in cell trafficking and development of various tissue and organs of immune system. Based on nature of synthesized cytokines during immune response there may be allergy, cytotoxic, cellular or humoral mediated immune response taking place.\[91\] Cytokines are messenger molecules that are able to help controlling the growth and activity of immune system cells.\[67\]

**Interleukins** are type of cytokine, a molecule produced by some immune cells to control the growth and activity of other immune cells. A man-made version of an interleukin, IL-2, is approved to treat advanced kidney cancer and metastatic melanoma. **Interferons** are type of cytokine that can change the way your immune system works. An interferon, INF-α is used to treat cancers.\[91\]

Recently approved CAR T-Cell Therapies:

**B-cell Acute Lymphoblastic Leukemia (ALL):** Tisagenlecleucel (Kymriah) is the first CAR T-cell therapy approved by FDA in August 2017 for children and young adults for an aggressive type of leukemia — B-cell ALL— that has resisted standard treatment or relapsed. CAR T-cell therapy was invented by a group of scientists, including Carl June from the University of Pennsylvania, about a half decade ago. It is the first-ever treatment that genetically alters a patient’s own cells to fight cancer, a milestone that is expected to transform treatment in the coming years. Tisagenlecleucel targets a protein, known as CD19, on malignant and normal B cells. In a clinical trial of children and young adults with relapsed or refractory ALL, cancer went into remission within 3 months of receiving tisagenlecleucel in 52 (82%) of 63 patients, and 75% of patients remained relapse free at 6 months.\[93\] This global clinical trial confirmed the high efficacy that was demonstrated in prior, single-institution trials; however, the rate of immune-related adverse effects was high with
tisagenlecleucel. Nearly 50% of patients experienced severe cytokine release syndrome (CRS), a complication during which CAR T cells produce a storm of inflammatory molecules.

**Large B-Cell Lymphoma**

CAR T cells that target CD19 have also been proven to be promising against another hard-to-treat cancer, diffuse large B-cell lymphoma (DLBCL), which is the most common type of non-Hodgkin lymphoma. On October 18, 2017, the Food and Drug Administration granted regular approval to axicabtagene ciloleucel (YESCARTA) for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma. Approval was based on a single-arm multicenter trial of 108 adult patients with aggressive B-cell non-Hodgkin lymphoma. Eligible patients had refractory disease to the most recent therapy or relapse within one year after autologous hematopoietic stem cell transplantation. Patients received a single infusion of axicabtagene ciloleucel following completion of lymphodepleting chemotherapy. The objective response rate (ORR) was 72%, with a complete remission (CR) rate of 51%. The most common adverse reactions (incidence of 10% or greater) include febrile neutropenia, fever, cytokine release syndrome (CRS), encephalopathy, infections, hypotension, and hypoxia. Serious adverse reactions occurred in 52% of patients and included CRS, neurologic toxicity, prolonged cytopenias (including neutropenia, thrombocytopenia, and anemia), and serious infections.

**CONCLUSION**

Decades of research on the biology of cancer have revealed insights into the mechanism that drives again. These efforts include the development of more effective and less toxic treatments, such as targeted therapies, immunotherapies, and cancer vaccines, as well as the improvement of therapies that have existed for decades, such as chemotherapy, radiation therapy, and surgery. Over the last few years, there has been a wave of new successes with immunotherapy. Research has proven this approach can be effective against a wide range of hard-to-treat advanced cancers previously considered intractable. Researchers are now working to identify biologic markers that can help increase the effectiveness of treatment and determine who is most likely to benefit from immunotherapy. This knowledge will enable oncologists to make evidence-based decisions so as many patients as possible might benefit.
from this new type of treatment. The development of biomarkers might predict whether immunotherapy can work well in individual patients and enable more personalized treatment.

After decades of research, the powerful and decidedly unique way of treating cancer, that is, adoptive cell therapy has become available to certain patients with an otherwise incurable blood cancer. In August 2017, the historically significant FDA approval the first adoptive cell immunotherapy, also known as chimeric antigen receptor (CAR) T-cell therapy, and the first gene therapy for cancer, tisagenlecleucel is the medical need this unique new therapy is poised to fill. The other first among FDA approvals in 2017 that marks a milestone in precision oncology is the accelerated approval of immune checkpoint inhibitor pembrolizumab to treat any type of solid tumor that has mismatch repair deficiency, a defect that undermines the cell’s ability to repair DNA damage. The volume and pace of cancer research is growing rapidly. Yet more work lies ahead. Many people are still waiting for the next breakthrough in cancer.

REFERENCES


15. Cancer control: knowledge into action: WHO guide for effective programmes; module 4-Diagnosis and Treatment.


43. Tan, Benjamin MD; Piwnica-Worms, David MD, PhD; Ratner, Lee MD, PhD, Multidrug resistance transporters and modulation, Current Opinion in Oncology; September 2000; 12(5): 450-458.


