CHAPTER

CURRENT CANCER THERAPIES: FOCUS ON HYPERTHERMIA AND IMMUNOTHERAPY

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Poonam A. Bedge[1,#], Raghvendra A. Bohara[1,2,#,*], Pooja M. Patil[1], Meghnad G. Joshi[1] and Deepak A. Bohara[3]

[1]Centre for Interdisciplinary Research, D. Y. Patil University, Kolhapur, Maharashtra, India [2]CÚRAM, Centre for Research in Medical Devices, National University of Ireland Galway, Galway, Ireland [3]Department of Cardiology, Ozone Multispecality Hospital, Akola, Maharashtra, India

3.1 INTRODUCTION

Noncommunicable diseases (NCDs) are a huge cause of death worldwide, mainly due to cardiovascular diseases, chronic respiratory diseases, cancers, and diabetes. Due to NCDs more than 36 million die annually (63% of global deaths), before the age of 70 including 14 million individuals who die too young. In low- and middle-income countries more than 90% of these preventable premature deaths due to NCDs occur. The common risk factors include unhealthy diet, tobacco use, harmful use of alcohol, and physical inactivity, which lead to premature deaths. In 2015, 8.8 million deaths were due to cancer and globally it is second leading cause of death. In men the most common kinds of cancer are prostate, breast, colorectal, lung, colorectal, lung, stomach, and liver, while in women the most common cancers are lung, cervix, breast, colorectal, lung, and stomach [1]. Cancer refers to malignant neoplasms or tumors. Tumors are cells in a tissue that grow out of control. The tumor cells can be classified into two types: malignant and benign. In malignant tumors the tumor cells spreads to neighboring tissue and interfere with the normal function of tissue and often have undesirable effects. In the case of benign tumors there is an increase in cell growth due to continuous division, but they remain in the tissue.

Due to mutation or abnormal activation of cellular genes cancer is caused, and these genes are responsible for cell control, growth, and mitosis. These genes are called oncogenes. These genes are controlled by specialized genes called tumor suppressor genes. The normal function of these genes is to control this transformation of normal cells into cancer cells. There are numerous factors that activate the oncogenes and cause the transformation of normal cells to cancer cells. Fig. 3.1 depicts a flow chart suggesting the simplified scheme of cancer pathogenesis. Cancer can be classified into different types dependent on whether the tissue or cells are involved.

Table 3.1 deals with the classification of cancer, describing some common examples. The fundamental factor which also plays a vital role in the development of cancer is aging. With age the

*Corresponding Author: Raghvendra A Bohara
#First Author equal contribution: both RAB AND PAB Equally contribute to the chapter.

Hybrid Nanostructures for Cancer Theranostics. DOI: https://doi.org/10.1016/B978-0-12-813906-6.00003-2

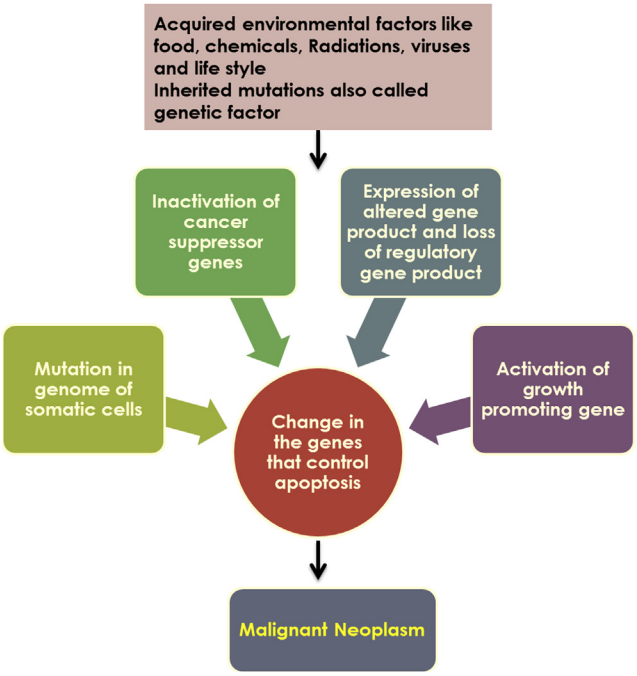


FIGURE 3.1

Two components are invariably involved in the pathogenesis of cancer. These are genetic factors and environmental factors. In most individuals both factors are relevant. This figure shows a simplified view of cancer pathogenesis. The different factors, including environment and life style disorders, can play a major role and lead to mutations in the genomes of somatic cells. All these factor lead to change in the genes, are responsible for apoptosis, and lead to transformation of normal cells to malignant cell.

incidence of cancer rises dramatically, due to a build-up of risk. The tendency and overall risk accumulation are combined so that as a person grows older their cellular repair mechanisms become less effective.

SOME KEY FACTS ABOUT CANCER ARE NOTED HERE [1,2]:

- 8.8 million people worldwide died from cancer in 2015;
- Approximately, 70% of deaths from cancer occur in low- and middle-income countries;
- Around one-third of deaths from cancer are due to the five leading behavioral and dietary risks: high body mass index, low fruit and vegetable intake, lack of physical activity, tobacco use, and alcohol use;
- Tobacco use is the most important risk factor for cancer and is responsible for approximately 22% of cancer deaths.

Cancer arises from the transformation of normal cells into tumor cells is a multistage process that generally progresses from a pre-cancerous lesion to a malignant tumor. These changes are the result of the interaction between a person's genetic factors and phenotypic factor.

Table 3.1 Classification of Cancer Based on Tissue of Origin

Type	Tissue or cell origin	Example
Carcinoma	Endoderm or ectoderm	Epithelial lining of gut (adenocarcinoma of colon or bronchus)
Sarcoma	Mesoderm	Osteosarcoma Fibrosarcoma
Leukemia	White blood cells	Acute lymphoblastic leukemia
Lymphomas	Monocytes	Hodgkin's diseases
	Macrophages	

THERE ARE SEVEN DANGER SIGNALS FOR CANCER:

- A sore throat that does not heal;
- change in the color of warts or moles;
- chronic indigestion or difficulty in swallowing;
- a lump or thickness in breast or any part of the body;
- change in normal bowel habits;
- persistent hoarseness.

3.2 CANCER: HISTORY AND LANDMARKS

There is a saying that cancer is as old as the human race, but paleopathology findings suggest that tumors were present in animals before they were seen in humans, but all this needs written proof, which appeared in 3000 BC in the Edwin Smith Papyrus in which was written the first description of breast cancer with the conclusion that this disease had no treatment [3]. Fig. 3.2b represents the Edwin Smith Papyrus about breast cancer and the collected writings of Hippocrates. Hippocrates and his followers tried to dispel the superstitions associated with cancer and explained its main natural causes. Later, Celsus, a Roman physician, followed the tradition of Hippocrates by comparing cancer with a crab that adheres to surrounding structures with its claws. He published his first book, "DeMedicina," on medicine (Fig. 3.3), in which he has tried to describe superficial cancer and cancers of visceral organs. He reported topical and surgical treatments in his book. He knew that in the armpit the advanced breast cancers tend to recur, without or with swelling of the arm, and that once spread to distant organs it may cause death [4–7] (Fig. 3.4).

Thereafter, there were numerous discussions about cancers, and each one has tried to explain this disease with his own understanding and possible treatment options. This information is summarized in tabular form along with the silent features (Table 3.2).

3.3 AVAILABLE CANCER TREATMENT OPTIONS

Over the past 250 years, numerous landmark discoveries have been witnessed in the progress against cancer, a disease that has been known as an affliction to humanity for thousands of years [13]. The knowledge on cancer initiation and progression, and the development of novel cancer treatments, has significantly increased, but only marginally improved patient survival. Surgery, chemotherapy, and

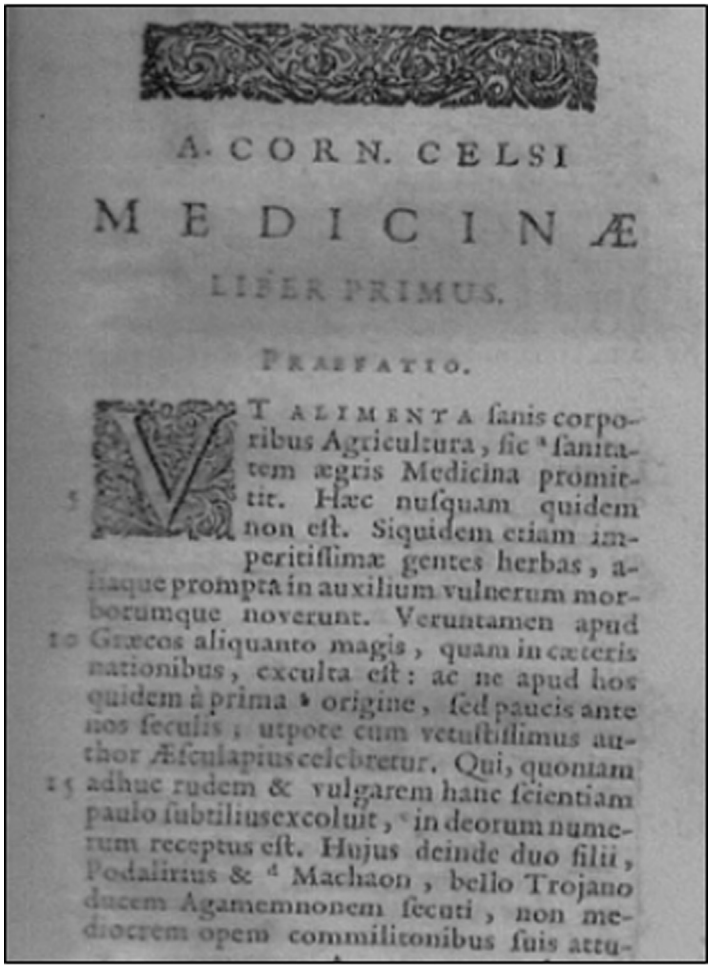
FIGURE 3.2

(a) The Edwin Smith Papyrus, written about 3000 BC contains the first written description of breast cancer. The writer concluded that there was no treatment for bulging tumor of the breast and that it is a grave disease. In Venice 1588, the writings of Hippocrates were printed. (b) In his collection he opposed superstitious causes of cancer. He and his followers have found that the cancer is initiated via natural causes. He explained that the deep and superficial cancers are separate entities and it was differently treated. The treatment of lotions and cautery were given to superficial lesions, and deep tumors were heat cut out with a knife or deemed untreatable [8]. Copyright 2011 Landmarks in History of Cancer, Part 1. Cancer.

radiotherapy are the most common types of cancer treatments available nowadays. In addition, stem cells, gene therapy, and immune therapies are being successful studied and seem to have a healthier role to play in the cancer treatment modality. In the case of solid tumors the choices of treatment into the 1960s were surgery and radiotherapy. However, due to uncontrolled metastasis, this led to a plateau in cure rates [14]. The next section deals with the newer treatment modalities that have been considered as potential options in cancer therapy and that hold promise in the battle of cancer.

3.3.1 IMMUNOTHERAPY

Coley's toxins and Erlich's hypothesis have suggested that cancer development is suppressed by the immune system [15,16]. Erlich's idea is expanded by Thomas and Burnet and they also proposed the immune surveillance hypothesis [17]. Main and Prehn [18] consequently demonstrated that carcinogens induce tumor-specific immune responses. In 1990, for superficial bladder cancer, guerin was approved [19], and for melanoma and renal cell carcinoma the improvement of cytokines interferon-α and interleukin-2 took place in 1986 and 1992, respectively [20]. Schreiber described immune editing as a process in which immune surveillance is escaped to establish overt malignancy [21]. In the last 10 years numerous specific cancer immunotherapies have been approved, including therapeutic and preventive cancer vaccines. Immunotherapy has become deeply rooted, and is the fourth most familiar term in cancer therapy, after chemotherapy, radiotherapy, and surgery. Apart from cancer this treatment is also used in allergies, and autoimmune and infectious diseases. The unique feature of cancer



A. CORN. CELSI

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FIGURE 3.3

The first edition of "DeMedicina" by Celsus. The book was printed in Florence in 1478, the first medical book printed. In this book Celsus described the different types of cancer and explained the early and aggressive surgical therapy for advanced-stage cancer [8]. Copyright 2011 Cancer.

immunotherapy is the universal power of treating the immune system across tumor types. Fig. 3.4 highlights the clinical success of immune checkpoint blockade (antagonists of PD-1, CTLA-4, and PD-L1). New dimensions have been added by immunotherapy to clinical practice, presenting much more specificity, directed therapy, higher efficacy, lower secondary effects, less toxicity, and better tolerance [22].

3.3.1.1 Components and classification of immunotherapy

In the immune system, natural killer (NK) cells, granulocytes, T and B lymphocytes, γδT cells, macrophages, and dendritic cells (DCs) are present. NK cells and granulocytes are "soldiers" of the

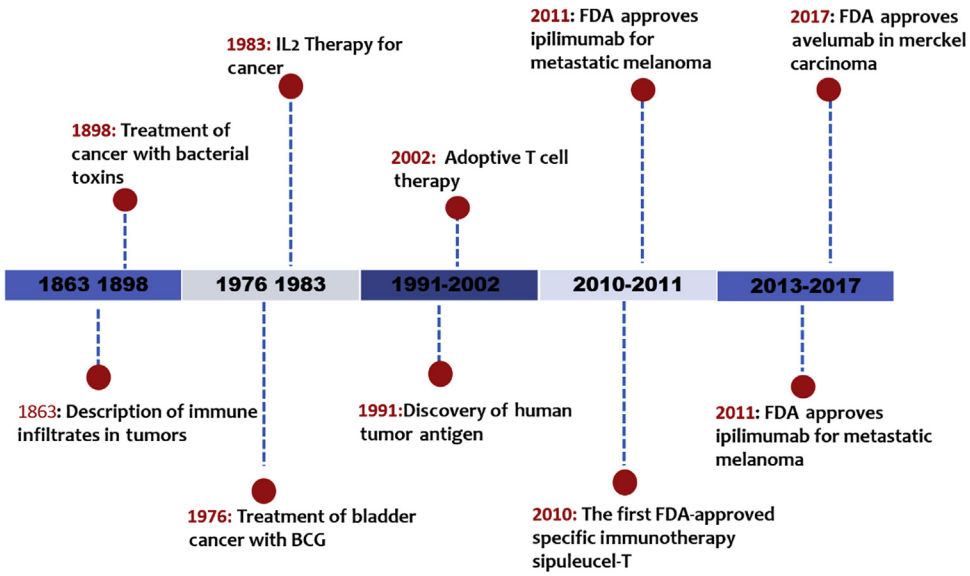

FIGURE 3.4

The history of cancer immunotherapy: from empirical approaches to current therapies. It also reveals the recent acceleration and expansion of cancer immunotherapy approvals. In a timeline illustrates regulatory approval in the United States since 2010 [23,24].

body and in an antigen-nonspecific manner they attack invaders. Macrophages are also present in specific organs and they process the information of antigenic invaders, old dying cells, injured cells, and mutated cells, locoregionally. T cells are antigen-specific and are further classified as helper T cells, regulatory T cells, cytotoxic T cells, inducer T cells, and suppressor T cells. They work under the directions of DCs and are heavily involved in tumor eradication. For antigen-specific antibodies, B lymphocytes function as a producer of antibodies after their differentiation into plasma cells after antigenic stimulation. DCs are identified as professional antigen-presenting cells. Immature DCs capture, process, and migrate antigens and are then differentiated into mature DCs in regional lymph nodes, where they present antigenic information to antigen-reactive T cells, resulting in T-cell activation in an antigen-specific manner. In the antigen-specific machinery of immune responses, DCs play a crucial role. Intercellular communications, such as inhibitory or stimulatory signals, are mediated by cytokines. Numerous cytokines have been identified to date, including interleukins, interferons, tumor necrosis factor, colony-stimulating factors, growth factors, etc. Cytokines are toxic to cancer cells but few cytokines are approved for use in cancer treatment. Antigen peptides are a part of the antigenic mother protein. They can stimulate antigen-reactive T-cell precursors in regional lymph nodes to become effector T cells, which then migrate to a target site and recognize the antigenic epitopes on target cells, including cancer cells. Many clinical trials using antigen peptides are now being conducted to determine the potential clinical benefits. These immune molecules function in the immune system through their specific receptors. Antigen peptides are recognized by T-cell receptors (TCRs) specific to the antigen. A BCR is a receptor on B

Table 3.2 Major Discoveries Related to Cancer Along with Salient Features

Name of the inventor	Salient feature	References
Pliny the Roman (AD 23−79)	Recommended herbal remedies for internal use in advanced cancer before or after attempted surgery. In his book, called Materia Medica, his most highly praised prescription was a boiled mixture of ash of sea crabs, egg white, honey, and powdered feces of falcons	[9]
Aretaeus (AD 81−138)	In his notes he reported two distinct forms of cancer: non-nucleated and ulcerated forms. This tumor is associated with pain and swelling in the groin	[9]
Claudius Galen (130−200)	He wrote that black bile caused ulcerated and incurable cancer, whereas thin yellow bile was responsible for nonulcerated and curable cancer. He supported surgical treatment as the best option for cancer therapy	[4]
Aetius (527−565)	Amputation of the whole breast	[4,10]
Avicenna of Persia (980−1037)	Introduced polypectomy by a wire loop that was made tighter each day until the tumor fell off	[11]
Lanfranc (1252−1315)	The first description is given by him about how to differentiate benign tumors of the breast cancer. Surgeons are advised by him to study about the complex anatomic setting of vessels and nerves before they operate. Lanfranc summarized his thoughts in his texts, Chirurgia Parva and Chirurgia Magna	[4,10]
Guy de Chauliac (1300−1368)	Wrote a chapter in his book Chirurgia Magna, on skin diseases and cancers	[12]

cells, a molecule of which is an antibody, as mentioned above. In addition, toll-like receptors are molecules that transduce danger signals of invaders into immune cells. Each cytokine has a corresponding receptor on the cell surface, through which functional signals are transduced into the cells. When we classify the current types of cancer immunotherapy, two nomenclatures of immunotherapy types are used: active immunotherapy and adoptive immunotherapy [25]. Active immunotherapy includes cancer vaccines, where therapeutic vaccines indirectly attack tumor cells with the emergence of immune activation specific to tumor antigens. Immune cells that are stimulated and activated by the cancer vaccines "actively" function in tumor eradication in a host. In terms of an "indirect" working property, the immune checkpoint inhibitors described below can also be considered to belong to the active immunotherapy category. In contrast, adoptive immunotherapy is a treatment using tumor-reactive immune molecules (cytokines or antibodies) or cells, which themselves directly attack tumor cells for eradication. When treating a host undergoing cancer immunotherapy, more attention must be paid to the patient's immunocompetency in active immunotherapy compared to adoptive immunotherapy [26,27] (Fig. 3.5).

By using tumor-reactive immune molecules (antibodies, cells, or cytokines) adoptive immunotherapy treatment is given, from which eradication occurs by attacking tumor cells.

3.3.1.2 Cancer immunotherapy has unique patterns of clinical benefit

Immunotherapy has an impact on overall survival in a paramount way. Ipilimumab was approved by the FDA in 2011 against melanoma cancer. This drug acts by directing cytotoxic T lymphocytes

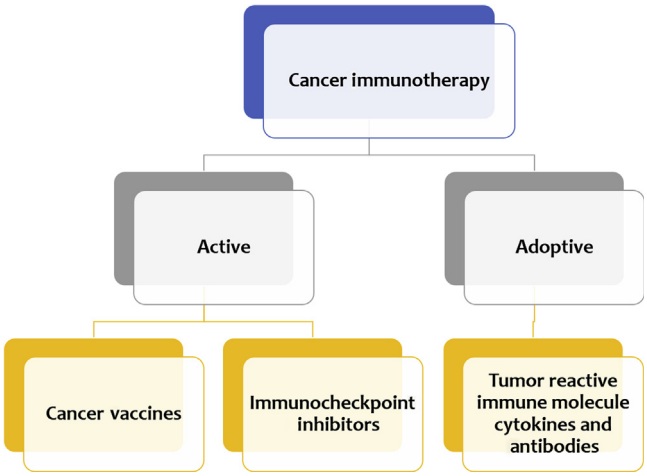

FIGURE 3.5

The classification of immunotherapy. Cancer vaccines and therapeutic vaccines are included in active immunotherapy specific to tumor antigens with the emergence of immune activation that indirectly attacks tumor cells. Immune checkpoint inhibitors are the protein which alter the immune response. Immune checkpoints can be stimulatory or inhibitory. Tumors can use these checkpoints to protect themselves from immune system attacks. Inhibitory checkpoints, restoring immune system function, can block by checkpoint therapy. On T cells or cancer cells, examples of checkpoint proteins are found: CTLA-4/B7-1/B7-2 and PD-1/PD-L1. For treatment of cancer many immune checkpoint inhibitors are used.

associated protein (CTLA-4). Cancer cells are recognized and destroy by cytotoxic T lymphocytes (CTLs). This destruction is interrupted by an inhibitory mechanism. This inhibitory mechanism is turned off by ipilimumab and allows CTLs to function. With advanced melanoma the meta-analysis of 5000 patients showed that the chronic disease is avoided by 20% of patients with ipilimumab [28]. Earlier data indicated that single-agent nivolumab [29–31], combined with ipilimumab/nivolumab [32] and pembrolizumab [33], will have a more long-term effect with PD-1 antagonists. In the long-term responders, PD-1/PD-L1 blockade appeared to double in number comparative to CTLA-4 blockade [34,35]. (Fig. 3.6).

- Programmed death-ligand 1 and programme cell death protein (PD-1 inhibitors and PD-L1) inhibitors are a group of checkpoint inhibitors being developed for the treatment of cancer. This is the protein present on the surface of the cells.
- The interaction of PD-L1 on tumor cells with PD-1 on a T-cell reduces T-cell function signals to prevent the immune system from attacking the tumor cells.
- Use of PD-1 and PD-L1 inhibitors blocks the interaction of PD-L1 with the PD-1 receptor and can prevent the cancer from evading the immune system in this way.
- Nivolumab and pembrolizumab are FDA-approved PD-1 inhibitors, while atezolizumab, avelumab, and durvalumab are FDA-approved PD-L1 inhibitors.

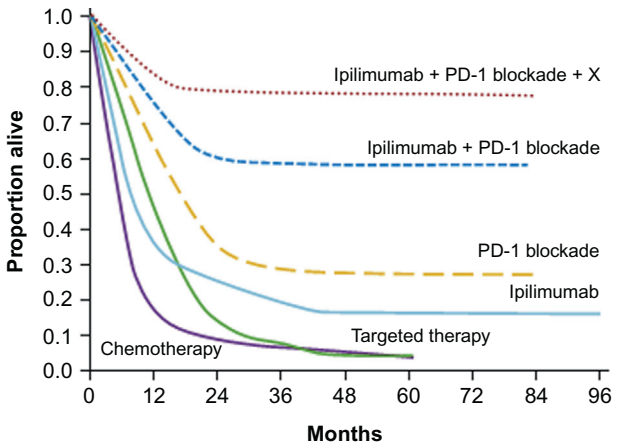

FIGURE 3.6

A model illustrating the potential impact of single agents and combination cancer immunotherapies on survival. Cancer treatment regimens that include immunotherapy can raise the tail of the curve, increasing overall survival relative to standard cancer therapies. Targeted therapies enhance response rates relative to standard chemotherapies, but overall survival is minimally impacted. Single-agent immunotherapy is associated with long-term survival rates ranging from 10% (ipilimumab) to 20–30% (PD-1 blockade). Combination immunotherapy targeting the CTLA-4 (ipilimumab) and PD-1 pathways (nivolumab/pembrolizumab) is associated with long-term survival rates of 50–60%. Third-generation combination immunotherapy regimens (illustrated as ipilimumab þ nivolumab þ X) have the potential to further maximize overall survival, moving closer to cure [34]. Copyright: Lancet.

3.3.1.3 Current clinical challenges

New clinical questions have been generated by the success of immunotherapy, including whether the use of immunotherapy is appropriate or not in earlier-stage disease, duration and schedule, optimizing dose, the impact of early treatment on overall survival, the development of novel surrogate endpoints, and the best biomarkers for patient selection that reflect the impact of immunotherapy [36].

3.3.1.4 A forward look at the role of immunotherapy

In the next 5–10 years, focus will be given to the clinical research and with synergistic antitumor activity, new combinations will be assessed to reduce toxicity. If the objective of cancer immunotherapy is to accomplish minimal toxicity with durable tumor eradication, before that promise can be realized numerous challenges and obstacles must be overcome. A major challenge is for the development of targeted immunotherapy identification of the appropriate tumor. For tumor cell growth and survival, the ideal tumor antigen is essential and specific, but for each individual tumor this can be different. Cell surface antigens are associated with numerous mAbs and CARs that target the tumor, but because of this normal cells are also destroyed (e.g., CD19-positive B cells or CD20, which are no longer expressed by tumor variants) [37]. For tumor

survival it is essential to the target tumor antigen, to decrease the effect of immunoediting. A few specialized cancer centers are integrated into routine outside clinical practice, as effective immunotherapies are becoming widely available. To predict the response to immunotherapy to identify biomarkers it is very important that patients are also identified who are likely to benefit. For example, positive tumor PD-L1 selection for treatment with a PD-1 or PD-L1 inhibitor has emerged as a rational strategy, but the response to ipilimumab has been elusive by a reliable predictive biomarker. Maximizing the number of patients is another challenge to achieving a robust benefit from immunotherapy [38]. The combination of PD-1/PD-L1 inhibitors with CTLA-4 inhibitors may move us nearer to achieving that objective, and combinations of targeted agents with immune checkpoint inhibitors could present the amount of checkpoint inhibition required for each individual patient, and optimize the balance between toxicity and efficacy in at a given time point of the disease [38].

3.3.2 HYPERTHERMIA THERAPY

Cancers are characterized by their unregulated growth and spread of cells to other parts of the body through the bloodstream or the lymphatic system [39]. Once the malignant cells deposit or start to form, leading to chaotic vascularization, new blood vessels grow (angiogenesis), unlike normal tissue. Due to defective blood perfusion, low pH and low oxygen pressure (hypoxia) occur in tumors and neighboring tissues. In these circumstances, anticancer drugs in a much lower concentration reach the affected regions than the aimed therapeutic dose and this situation also becomes problematic in delivering radiotherapy [40]. To improve this therapeutic approach, clinical hyperthermia, whereby temperature within the body is elevated to kill or damage malignant cancer cells, is a comparatively attractive approach. As an adjunct to chemotherapy and radiotherapy it has previously been used with success, and has synergistic effects [41–43]. Fig. 3.7 describes different ways that hyperthermia and heat therapy can be given.

Since 300 BC, it has been common practice to treat certain disorders with the application of hyperthermia [44]. In the last two decades the methodology of adjuvant treatment and its integration with current treatment has resulted in better results. The mutual efforts of experts in medicine, chemistry, physics, and engineering have played a crucial role, as reflected by the numerous reviews on the matter [45–49]. There are two reasons for these emergent collaboration networks. Primarily, due to nanotechnology incorporation and technique interpretation, for better localization of tumors and access to regions difficult to reach within the human body, are currently possible. Secondly, the new technologies and materials have shown promising results in clinical trials dealing with different stages kinds of cancer have been encouraged by the growing interest in hyperthermia, showing superior survival rates [50]. The next section deals with the effects of hyperthermia, mainly as a mechanism of cell killing. Fig. 3.8 deals with the synergistic effects of hyperthermia and standard cancer treatments, such as radiation and chemotherapy, in destroying tumor cells.

3.3.2.1 Thermal effects of the hyperthermia temperature range

In hyperthermia, the temperature ranges from 40 to 45°C, at which different types of cell death may be induced, and the treatment is designed dependent on the cell type and temperature.

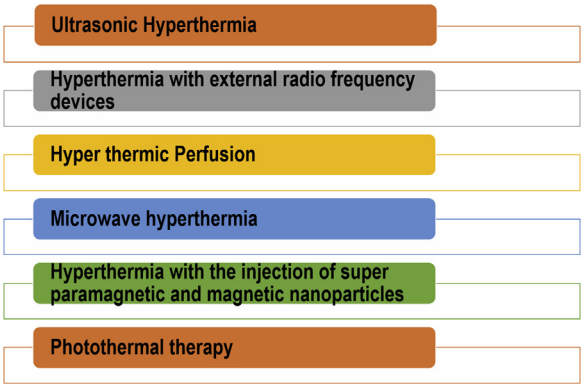

FIGURE 3.7

Different methods are used to initialize hyperthermia. Ultrasonic hyperthermia uses ultrasonic sound waves which range between 2 and 200 MHz. In the case of radio frequency, 8 MHz RF capacitive heating is used to generate the heat. The hyperthermic perfusion uses a procedure in which a warmed solution containing anticancer drugs is used to bathe, or is passed through the blood vessels of, the tissue or organ containing the tumor. Microwave hyperthermia uses microwave energy in effective heating of cancerous tumors. Microwave antennae are used to treat tumor, depending on tumor size and location in the body. Microwave hyperthermia has utilized single-waveguide microwave antenna working at 2450 MHz. In the case of magnetic materials, superparamagnetic iron oxide nanoparticles are used to generate the heat due to possible losses. Photothermal therapy refers to the use of infrared wavelengths by which the material is excited and heat is generated. This therapy is the extension of photodynamic therapy in which the photosensitizer is used.

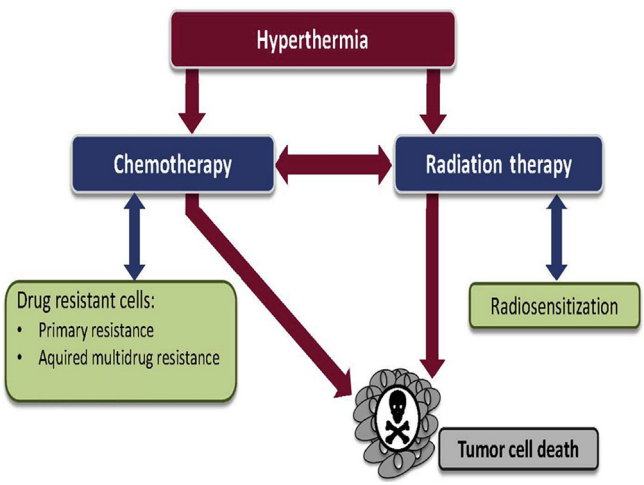

FIGURE 3.8

The synergistic effect of hyperthermia and standard cancer treatments, such as radiation and chemotherapy, in destroying tumor cells [43]. Copyright: 2013 InTech.

Apoptosis and mitotic catastrophic mitosis are types of cell death induced by hyperthermia (the cell is destroyed during mitosis in mitotic catastrophic events). Due to the combination of death processes most cell lines die. Locating the molecular mechanisms by which heat destroys tumor cells is one of the objectives of hyperthermia research [51–54]. To find out the exact effect of hyperthermia is difficult as it works at the cellular level and causes various macromolecular changes at temperatures above 42°C. In a variety of ways cells respond to stress that promotes survival by eliciting programmed cell death with activation of pathways that eliminate damaged cells. There is equilibrium between the net rate of cell death and the net growth rate during tissue homeostasis. Physiological homeostasis is in danger during exposure to cellular stress. Depending upon the severity and types of cellular stress, the cell's response varies. Beyond a certain threshold, if the stress stimulus does not disappear, with appropriate protective cellular response the cell will cope and cell survival is ensured. Conversely, failure to maintain or activate a protective response, for example with a stressful agent that is too strong, results in stress signaling cascade activation, which ultimately results in cell death [55]. One of the most important prosurvival activities of cells, the response to heat shock, as the biochemical response to heat stress has been described [56,57]. Evolutionarily conserved proteins, which are a set of heat shock proteins (Hsps), are grouped into subfamilies by molecular weight: 15–30, 40, 60, 70, 90, and 110 kDa. In these stresses, protein damage is the main cellular consequence, leading to the aggregation of unfolded proteins. To counteract this, Hsps protein expression is increased by cells to help the misfolded proteins to refold and protein aggregation to alleviate it. Transient protection is therefore conferred, leading to a state that is called thermo tolerance, whereby cells become more resistant to various stresses and are able to survive [55]. In the following section, different physiological and cellular effects of hyperthermia and their consequences are discussed in brief.

3.3.2.2 Hyperthermia and physiological effects

Some physiological factors, including pH, oxygen, and blood flow to hyperthermia were shown to have a role in the sensitivity of tissues/cells. In most research it is indicated that normal cells are less susceptible to heat injury than cancer cells. The differential expression of Hsps and other defenses play a vital role in protecting cells. Nevertheless, in findings about heat sensitivity between tumor cells and normal cells, there is no consistency. The sensitivity of cells to heat varies with the phase of the cell cycle, where cells in mitosis and S phase were reported to be more sensitive [43]. It is also known that in comparison to normal tissues, tumor tissues are poorly vascularized. This may tend to differential heating, compared with normal tissue higher temperatures bareeing achieved in tumors, as circulating blood heat is more dissipated. Tumors are not able to adapt their blood circulation to the effects of high temperatures above 42°C, which cut off the supply of oxygen and nutrients, leading to collapse of the tumor vasculature and lower interstitial pH [56]. These conditions render cells more susceptible. Certainly, cells at decreased oxygen tension and acidic (lower) pH, in the middle of tumors, are more sensitive to heat treatment [43]. In addition, another important aspect is that different elements of the immune system appear to be able to play a vital role in the temperature range of 40–41°C, thus immune surveillance increases. In temperatures ranging from ~42°C hyperthermia is capable of: (1) increasing the movement of immune cells, potentially not giving better control of infection and tumor burden; (2) cell surface molecules increasing the expression as well as being involved in effector activity

release of soluble factors; (3) proliferation of immune cell regulates; and (4) augmenting immune cells against target cells [57,58].

Yanase et al. observed that, using magnetic nanoparticles, tumor-specific hyperthermia-induced antitumor immunity. Their research revealed that CD4- positive and CD8-positive T cells migrated to the tumor site with killing of cancer cells [59].

3.3.2.3 Hyperthermia and cellular changes

Hyperthermia-induced stress is one of the most important factors in protein damage, leading to unfolded proteins and aggregation. The effects of hyperthermia on proteins include exposing and unfolding hydrophobic groups, and due to the exposed hydrophobic group interactions, unfolded proteins aggregate. The effects of protein aggregation and unfolding will be throughout the cell, but within the nucleus it should have a significant impact because a large amount of DNA and a large number of proteins are packed within it. These proteins within the nucleus are responsible for proper processes of replication, transcription, and repair of DNA. Therefore, there will be critical consequences for these proteins and their function. Specifically, protein disruption involved in DNA replication tends to result in improper processing of nascent DNA fragments and replication fork stalling, causing chromosome aberrations, instability in the genome, segregation of improper chromosomes, and death of cells. Distraction of proteins present in DNA repair tends to increase in unrepaired DNA damage. Eventually, genomic instability and chromosome aberrations are contributed by unrepaired DNA damage [58–60]. Stability and fluidity of cellular membranes are affected by hyperthermia and obstruct the function of cell surface receptors in vitro and in transmembranal transport proteins. In hyperthermic cell death, membrane alterations represent a significant target, which is also endorsed from these findings. The change in membrane potential gives rise to elevated intracellular calcium and sodium, as well as elevation of potassium efflux [61]. Mitochondrial membrane potential also has significant disruption, which results in changes to the redox status of cells, leading to bursting of reactive oxygen species (ROS), also protein stability is altered by oxygen radicals to heat-induced protein unfolding rendering proteins sensitive. Proteins are destabilization by altered protein stability within the nucleus disrupting DNA repair, DNA segregation, and DNA replication [60].

3.3.2.4 Significance of cellular and physiological effect

Protein aggregation, unfolding, and oxidation have simultaneous effects throughout the cell and within the nucleus have a significant impact because of the large amount of DNA and the large number of proteins within it. This tends to result in permanent G1 arrest, mitotic catastrophe, and clonogenic loss, i.e., the reproductive capacity of cells. In addition, hyperthermia has a major impact on the transmembranal protein present and leads to altered membrane potential and generation, which results in the generation of ROS and is responsible for cell apoptosis [43,61–63]. It has been observed that in hyperthermia the intensity of cell death is cell cycle-dependent. In general, during S and M phases of the cell cycle, high heat sensitivity can be seen. Following hyperthermia, between the different cell cycle phases these variations exist, indicating the diversity of molecular mechanisms of cell death. Fig. 3.9 shows the effect of hyperthermia-induced changes which finally leads to cell death by apoptosis or necrosis.

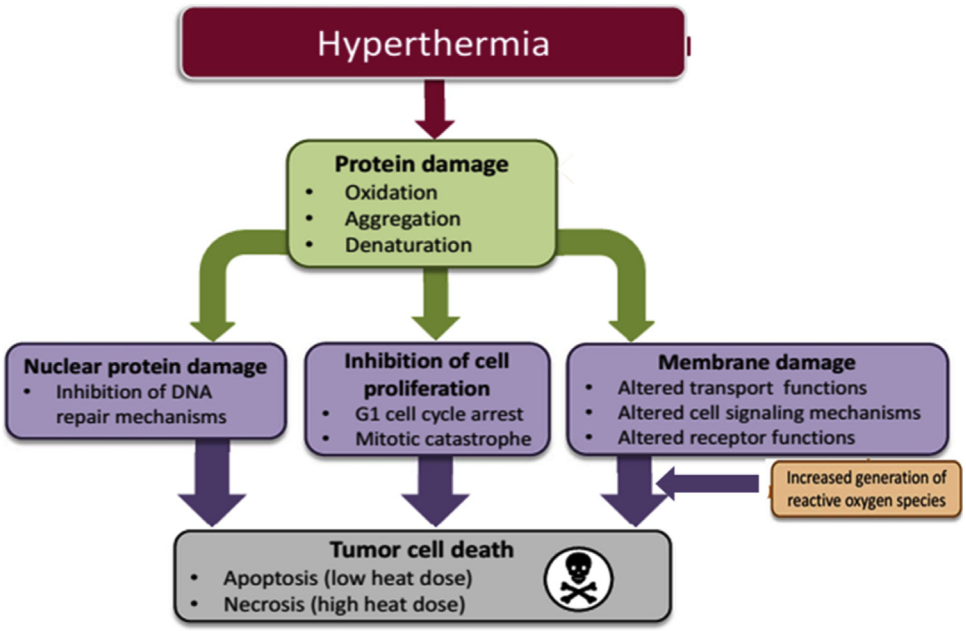

FIGURE 3.9

The effect of hyperthermia-induced multiple changes and finally leads to cell death by apoptosis or necrosis [43]. Copyright: 2013 InTech.

3.3.2.5 Clinical trials on hyperthermia

Many clinical trials are being conducted to evaluate the effectiveness of hyperthermia. Table 3.3 deals with the significant clinical trials that have taken place in the field of hyperthermia [64]. This treatment has been used along with conventional treatment modalities such as radiation and chemotherapy and in most cancers there were survival benefits.

3.4 COMBINATION THERAPY IS THE KEY TOWARD SUCCESS

Given the strong immunomodulatory response of nanoparticles, many immune adjuvant strategies have been explored since the late 1990s using both magnetic fields and laser-induced hyperthermia. This approach was tried using magnetic hyperthermia or laser hyperthermia. In the case of laser hyperthermia, a photosensitizer was used which was irradiated with light and could generate heat. In parallel, the group of Kobayashi et al. extended their localized hyperthermia approach using magnetite cationic liposomes in combination with interleukin-2 (IL-2) and granulocyte macrophage-colony-stimulating factor, illustrating in a preclinical melanoma model reduced tumor burden and increased survival for the combination of treatments over monotherapies alone [65]. These pioneering studies demonstrated the synergy between immune response from local heating and immune modulatory agents; however, the immunotherapies studied

Table 3.3 Clinical Trials of Hyperthermia [64]. Copyright: 2016 Achiev. Life Sci.

Cancer site	Control therapy	Experimental work done	Primary endpoint	Survival benefit
Head and neck (primary)	Radiotherapy	Radiotherapy and local hyperthermia	Response at 8 weeks	No
Melanoma	Radiotherapy	Radiotherapy and local hyperthermia	Complete response	No
Superficial (head, neck, breast, miscellaneous)	Radiotherapy	Radiotherapy and local hyperthermia	Initial response	No
Head and neck	Radiotherapy	Radiotherapy and local hyperthermia	Best response	Yes
Breast (advanced primary or recurrent)	Radiotherapy	Radiotherapy and local hyperthermia	Initial response	No
Breast cancer (phase III)	Radiotherapy	Radiotherapy and local hyperthermia	Disease-free survival	Yes
Superficial (head, neck, breast, sarcoma)	Radiotherapy 1 × local hyperthermia	Radiotherapy and local hyperthermia	Best response	No
Superficial (head, neck, breast, sarcoma)	Radiotherapy 1 × local hyperthermia	Radiotherapy and local hyperthermia	Initial response	No
Superficial (head, neck, breast, sarcoma, others)	Radiotherapy 2 × local hyperthermia	Radiotherapy and local hyperthermia	Initial response	No
Glioblastoma	Radiotherapy interstitial radiotherapy	Radiotherapy, interstitial radiotherapy, and interstitial hyperthermia	2-year survival	Yes
Rectum (T4 locally advanced)	Radiotherapy	Radiotherapy and endocavitary hyperthermia	Initial response	Yes
Esophagus (stages I–IV, neoadjuvant)	Radiotheraphy and chemotherapy	Radiotheraphy, chemotherapy, and endocavitary hyperthermia	Histological complete response	Yes
Esophagus (stages I–IV, neoadjuvant)	Chemotherapy	Chemotherapy and endocavitary hyperthermia	Initial response	Yes
Stomach (T3, locally advanced)	Surgery	Surgery and hyperthermic intraperitoneal perfusion	5-year survival	Yes
Melanoma (stages I–III)	Surgery	Surgery and hyperthermic isolated limb perfusion	Disease-free survival	Yes
Melanoma (stages I–III)	Surgery	Surgery and hyperthermic isolated limb perfusion	Disease-free survival	No
Primary or recurrent pelvic (cervix, rectum, bladder)	Radiotherapy	Radiotherapy and regional hyperthermia	Complete response	Yes
Localized tumor (phase III)	Radiotherapy with superficial hyperthermia	Radiotherapy with superficial hyperthermia	Partial response	Yes

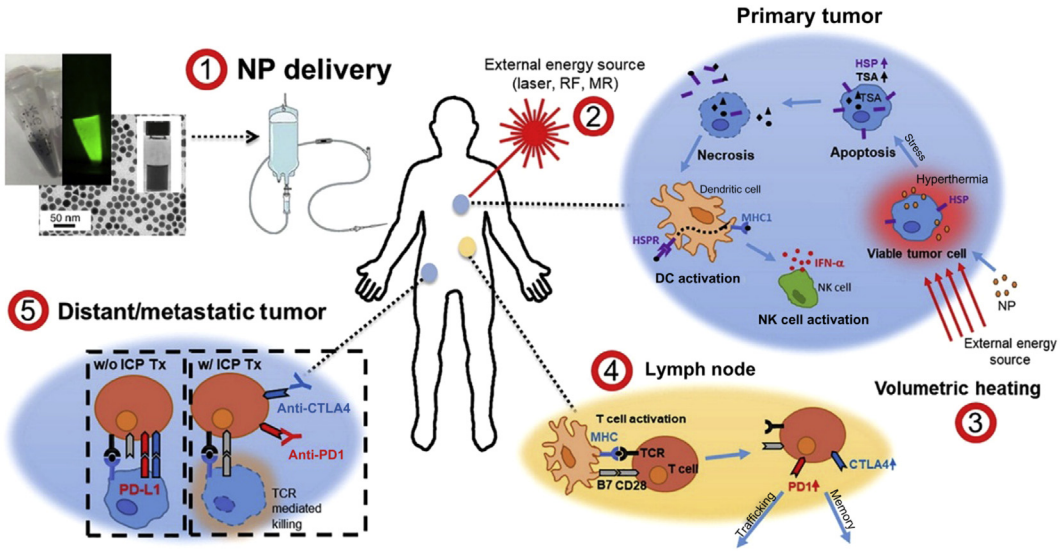

FIGURE 3.10

Combination therapy in treatment of the cancer. The combination of magnetic nanoparticles and immunotherapy for cancer. (1) Systemic administration of nanoparticles that localize to the tumor and (2) irradiation with an external energy source are the main components of NPHT. (3) Tumor hyperthermia initiates the apoptosis responses that upregulate tumor-specific antigens (TSAs) and expression of heat shock proteins (HSPs). Necrosis releases TSA and HSP−TSA complexes that activate antigen-presenting dendritic cells (DCs). HSP receptors (HSPRs) on DCs recognize HSP−TSA complexes, activating natural killer (NK) effector cells and release of cytokines and chemokines. (4) DCs traffic TSA to the lymph nodes (LN) where they activate T cells with T-cell receptors (TCRs) specific to the TSA. Activated T cells upregulate inhibitory surface receptors (PD-1 and CTLA-4), and (5) traffic back to the primary and distant/metastatic tumors throughout the body, initiating TCR-mediated killing of tumor cells. In the absence of ICP therapy, inhibitory ligands on the tumor cells (e.g., PD-L1) would downregulate and inhibit a full response; however, blocking the immune checkpoints allows for a full, uninhibited immune response, ultimately resulting in tumor cell killing and immune memory [66]. Copyright: 2017 Adv Drug Deliv Rev.

have not yet achieved widespread clinical use. Fig. 3.10 explains combination therapy in the treatment of cancer, including the combination of magnetic nanoparticles and immunotherapy for cancer.

ACKNOWLEDGMENT

Raghvendra Bohara is thankful for Irish Research Council for the financial support under the Government of Ireland Postdoctoral fellowship grant GOIPD/2017/1283. Raghvendra Bohara also likes to acknowledge Science Foundation Ireland (SFI) and is cofunded under the European Regional Development Fund under grant number 13/RC/2073.

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