Review Article

Anticancer therapeutics: a brief account on wide refinements

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Abstract: The fluctuating rise in cancer incidence along with treatment anomalies has made cancer the second leading cause of death globally. The total annual economic impact of cancer is pronounced and is increasing. Besides the lack of proper curative therapy, treatment associated adverse effects, drug resistance, and tumor relapse are the instigations behind increased morbidity and mortality. Meanwhile, the survival rate has inclined impressively. In the last few decades, cancer treatment has undergone wide refinements aiming towards cancer prevention, complete tumor regression, subsiding treatment adverse effects, improving patient’s life standard and avoiding tumor relapse. Chemotherapy has been successfully extended towards natural, cheaper and bioactive anti-inflammatory agents manifesting potent anticancer activity. Antibody-based cancer therapy has become well established as a vital and effective strategy for treating hematological malignancies as well as solid tumors. Individualized immunotherapy is becoming the forefront of cancer treatment enabling personalized, precise and patient’s cancer mutanome specific adjustable regimen. The emergence of anti-neoangiogenesis and cancer stem cell targeting techniques have dropped cancer recurrence significantly. Advancements in hyperthermia and photodynamic therapies along with improvements in cancer vaccination have declined death rate and amplified survival rate convincingly.

Keywords: Anticancer therapeutics, cancer targeting, conventional and non-conventional chemotherapy, hyperthermia treatment, photodynamic therapy (PDT), monoclonal antibodies (mAb’s)

Introduction

According to WHO one in every six deaths is caused by cancer [1]. Being the second leading cause of death, cancer is responsible for an estimated 9.6 million deaths worldwide in 2018 [1]. Every four minutes, someone dies from cancer in the UK [2]. Approximately 70% of deaths from cancer occur in middle and low-income countries. The total annual economic impact of cancer is pronounced and is increasing. The estimated economic cost of cancer in 2010 was approximately 1.16 trillion US$ annually. Additionally, a study in 2008 reported that 12.7 million new cases of cancer were identified worldwide, and it was projected that 15-17 million new cases would be identified by 2020 [3]. In accordance, there were 17 million new cases in 2018 and the number is estimated to rise to 27.5 million per year by 2040 [3].

A cancerous cell, after gaining sufficient genetic and epigenetic mutations, replicates at higher rates as compared to the normal cell and establishes a surrounding tumor microenvironment. This microenvironment is crucial for growth, proliferation, and migration of cancer cells [3-6]. The primary technique to fight cancer is believed to be the removal of the cancerous tumor through clinical surgery but with some unwanted side effects. Besides, several other therapies like radiotherapy, immunotherapy, chemotherapy, photodynamic therapy, hyperthermia, non-traditional therapy with natural bioactive materials and tumor vaccination are also in practice, improving and adapting continuously to clinical needs [7, 8]. The radioimmunotherapy includes the exploitation of immune proteins as radioactivity carriers or as targeted therapeutics [9, 10]. A wide range of chemotherapeutics are used to treat cancer, but they lack obligatory selectivity leading to adverse or side effects [11]. Nanomaterial based drug delivery system is emerging as a promising approach to overcome this problem [12] it involves solid gold nanoparticles [13,
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Table 1. Different monoclonal antibodies (mAb’s) based anticancer therapeutic approaches and their target antigens [45]

<table>
<thead>
<tr>
<th>Monoclonal antibodies-based therapeutics</th>
<th>Design</th>
<th>Target antigen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antitumor mAb’s</td>
<td>Modified or unmodified IgG</td>
<td>Tumor specific surface antigens</td>
</tr>
<tr>
<td>Radioimmunotherapy</td>
<td>Unmodified IgG or specific mAb’s fragments</td>
<td>Tumor specific surface antigens that are not shed in the systemic circulation</td>
</tr>
<tr>
<td>Antiangiogenesis</td>
<td>Unmodified IgG</td>
<td>Angiogenic host molecules</td>
</tr>
<tr>
<td>T-cell checkpoint blockade</td>
<td>IgG1 and IgG4</td>
<td>Anticancer T-cell suppressors</td>
</tr>
<tr>
<td>Antibody and drug conjugate</td>
<td>Drug and IgG linked through a linker for tumor specific drug delivery</td>
<td>Tumor specific surface receptors capable of internalizing mAb and associated drug molecules</td>
</tr>
<tr>
<td>Chimeric antigen receptor T-cell</td>
<td>Modification of T-cells for producing mAb’s specific regions through DNA modification (Gene therapy)</td>
<td>Highly tumor specific surface antigens in non-resistant as well as resistant tumors</td>
</tr>
<tr>
<td>Bispecific antibody</td>
<td>T-cell receptors activating and specific regions of cancer specific mAb’s</td>
<td>Tumor associated specific antigens</td>
</tr>
</tbody>
</table>

14], silver nanoparticles [15], iron oxide nanoparticles [16-18], carbon nanotubes [19, 20], quantum dots [21-23], liposomes [24, 25], niosomes [26-28] and dendrimers [29-31]. These nano-carriers are of great advantages like the improvement in drug solubility and reduced metabolism, increased circulation time and delivery and comparatively higher accumulations in specific tumors [32, 33].

Extensive research is done to explore better prospects or refine the current anti-cancer treatment protocols. Cancer treatment is advancing continuously, the death rate has declined, and the survival rate has been improved convincingly. For instance, the cancer survival rate in the UK has doubled in the last 40 years [2]. In the US, five years the combined survival rate for all childhood cancers has inclined to 81% compared to 62% in 1976 [34]. In the last two decades, cancer treatment has undergone wide refinements aiming towards cancer prevention, complete tumor regression, subsiding treatment adverse effects, improving patient’s life standard and minimizing tumor relapse. The review further describes a brief review of advancements and developments in some major anticancer therapies in the recent past.

Therapeutic strategies

Monoclonal antibodies

Monoclonal antibodies (mAbs), replicates of one type of antibody, that identifies and attaches itself to a specific protein produced by the cells. Depending on the targeted protein, mAbs can work in different ways and can be used to treat different types of cancer [35-37]. Over the past 20 years, antibody-based cancer therapy has become well established and it is now one of the most important and effective strategies for treating patients suffering from hematological malignancies and solid tumors (Table 1) [38-40]. Antibody-based cancer therapy dates back to the original interpretations of antigen expressions by tumor cells through serological techniques in the 1960s [41]. The cell surface antigens expressed by human cancer cells have revealed a broad range of overexpressed targets, mutated or selectively expressed in comparison to normal tissues [42]. The identification of suitable antigens for antibody based therapeutics is a crucial task and can act through interceding modifications in the fundamental functions of antigen or receptor and modulation in the immune system or transportation of a specific drug moiety conjugated to an antibody targeting a particular antigen [43, 44]. According to some in vitro and animal studies, mAbs targeting malignant cell surface antigens induce apoptosis through direct transmembrane signaling [45]. The target cancerous cells are also killed by mAbs via complement-mediated cytotoxicity [46] and through inducing antibody dependent cellular toxicity [47]. Bujak et al., with the help of phage display technology generated a human DLK1 specific antibody. Human normal adult tissues and human xeno-grafted tumors frozen sections were used to characterize DLK1 expression using this reagent. Nude mice were injected with radioiodinated preparations having SIP (F8) and SIP (EB3) with pre-subcutaneously grafted U87 tumors (Figure 1), where neoplastic lesions failed to be detected by IV administration of SIP (EB3) after 24 h. It was observed that the placenta developed a weak expression unlikely in
most of the organs where DLK1 was undetectable. It was also found that 8 out of 9 tumor types showed a moderate to strong expression. It was suggested that in the light of limited expression of proteins in normal tissue while abundance in the interstitium of neoplastic lesions, DLK1 might be a good target for antibody-mediated pharmaco-delivery strategies [48].

Tyrosine kinase which belongs to human EGF receptors (HER) acts as the main target for cancer therapeutics with specificity to HER2 and EGFR because of their in tumor genetic aberrations [49]. The overexpression of HER2 could be correlated with many adverse prognostic features like lower steroid hormone receptor expression, large tumor size, and aneuploidy, etc. [50-52]. Amplification of the HER2 gene is an autonomous adverse prognostic factor [53-56]. Trastuzumab (a recombinant monoclonal antibody against HER2) proved to be of clinical significance in first line chemotherapy against breast cancer by achieving a prolonged disease progression time (median, 7.4 vs. 4.6 months; P<0.001), prolonged response duration (median 9.1 vs. 6.1 months; P<0.001), enhanced objective response rate (50% vs. 32%; P<0.001), lesser death rate at 1 year (22% vs. 33%; P = 0.008), prolonged endurance (median, 25.1 vs. 20.3, 20.3 months; P = 0.046) as well as 20% death risk reduction. Cardiac dysfunction was found to be the most adverse event that occurred in 27% of group given trastuzumab, anthracycline, and cyclophosphamide; 8% of the group with cyclophosphamide and anthracycline; 13% of group given trastuzumab and paclitaxel and 1% of the group delivered with alone paclitaxel. Cardiotoxicity could be covered by proper medical management [57]. Gaborit et al., generated some monoclonal antibodies to HER3 and studied their effect on the degradation of HER3, growth inhibition of cultured cells and also the selection of most potent pancreatic cancer cells inhibitor. It was predicted that in comparison to the mechanism

Figure 1. (A) Showing BIAcore Profiles for SIP antibody and anti DLK1 scFv antibody against human DLK1-Fc recombinant fusion protein (B) SIP (F8) and SIP (EB3) radio-iodinated preparations. The results are shown as injected dose % per tumor tissue gram (% ID/g). Adapted From [49].
of anti-EGFR antibodies commonly used in the treatment of colorectal cancer, the anti-HER3 antibodies might be able to strongly inhibit tumor growth by intercepting autocrine and stroma-tumor interactions. The anti-HER3 Abs proved to be a better option instead of combing different Abs to enhance the anti-tumor effects of antibodies to NRG receptors [49]. The study proposed to strengthen the opportunity assigning NRGs receptors, HER3 as a powerful motivator in tumor progression as was suggested previously by [58-60]. Very recently some good work is on the way to treat cancer using monoclonal antibodies like phosphatidylserine targeting [61], inhibition of immunosuppressive human regulatory T cell activity by mAbs against GARP/TGF-B1 complexes [62] and anti-CD137 and adoptive T cell therapy [63].

Chemotherapy

Chemotherapy is one of the most widely used strategies for cancer treatment. Chemotherapeutic agents are vital in tumor regression and halting recurrence in more than 100 different known types of cancers [64, 65]. They are classified based on their modes of action to antimetabolites, antimicrobial agents, alkylating agents, antimetabolites, platinum complexes and antitumor antibiotics [64, 65]. Survival rates for malignancies are increasing with the advent of new modified chemotherapeutic treatments [66]. There are 400,000 malignancy survivors in the US [66]. However, despite enhanced efficacy and improved survival rates, side effects and long-term complications associated with chemotherapy are a major concern for patients, survivors, and clinicians [66, 67]. Data suggest that mortality and morbidity due to drug related adverse effects account for an estimated 6.5% of total hospitalizations [68, 69]. According to the FDA, 22 drugs used in cancer treatment are associated with more than 25 serious side effects including ulceration, anorexia, vomiting, central and peripheral neurotoxicity, malabsorption, anemia, weight loss, fatigue, chemotherapy induced diarrhea (CID) and constipation (CIC), enhanced risk of sepsis and chemotherapy induced peripheral neuropathy (CIPN). Studies demonstrate that survivors are at 8 folds higher risk of cardiovascular related problems leading to deaths, including coronary artery disease, myocardial infarction, congestive heart failure with cardiomyopathy and cerebrovascular event [66, 67, 69]. Knowing that almost 70% of deaths from cancer occur in lower- and middle-income countries, the cost associated with chemotherapy is itself a major concern further perpetuating the mater [3]. Scientists have been looking for new and better treatment approaches to combat this challenge by improving tolerance, minimizing the cost of treatment and limiting the sequelae of chemotherapy [66, 67]. Convincing reports in the literature, emphasize the use of natural cheaper bioactive compounds as non-traditional chemotherapeutic agents [67, 70, 71]. Moreover, their synergistic combination with traditional chemotherapeutic agents can limit chemotherapy related adverse effects, potentiate anti-cancer activity, may overcome drug resistance and decrease recurrence [67, 70, 72]. Some of the reported nutraceuticals include terpenes, mushrooms, flavonoids, curcumin and stilbenes [70]. Plenty of nutraceuticals manifest anti-inflammatory activity and might, not only limit the tumor growth but can also regress the tumor mass [73].

Inflammation and cancer

“Hanahan and Weinberg” described the hallmarks of cancer [74, 75]. These hallmarks are the biological capabilities of human cancer cells acquired during the multistep development of tumors. They include evading growth suppressors, sustaining proliferative signaling, enabling replicative immortality, resisting cell death, inducing angiogenesis, initiating invasion and enabling metastasis [74, 76]. Further progress enlists genome instability, deregulated metabolism, evading immune system and inflammation as the emerging hallmarks. Cancer cells with all these adverse capabilities ultimately orchestrate tumor microenvironment [74, 77].

Inflammatory cells are a vital component of the tumor niche or tumor microenvironment [78]. Inflammation stimulates neoplastic activities involving survival, growth, proliferation, and migration [78, 79]. Neoplastic cells have co-opted inflammatory receptors and signaling molecules producing an array of mitogenic chemokines and cytokines [78-82]. These chemotactants attract inflammatory factors that potentiate the inflammatory process. Some of the players of inflammation include mast cells, granulocytes, lymphocytes, macrophages, fibroblasts, and endothelial cells.
addition to infiltrating inflammatory cells, activated fibroblasts, macrophages and mast cells also secrete cytokines, chemokines, and proteolytic enzymes, initiating neangiogenesis and lymphangiogenesis [72, 73, 78, 83, 84]. Proteases promote the tumor cell escape into the surrounding tissues by disrupting the basement membrane surrounding tumor cells [84, 85]. Macrophages being one of the main players release pro-angiogenic factors stimulating neo-angiogenesis and lymph-angiogenesis, immune suppressors avoiding anti-tumor activities of the immune system, tumor cell guiding factors promoting metastasis and growth factors fostering growth and motility of tumor cells [81, 82, 84, 85]. These inflammatory factors potentiate survival, tumor growth, angiogenesis, fibroblast migration, invasion and metastatic spread [71, 78, 81, 82].

Moreover, inflammation can also lead to DNA damage through reactive oxygen species (ROS) and reactive nitrogen species (RNS) induction causing both epigenetic alterations and mutations [86, 87]. ROS and RNS are produced locally by various inflammatory mediators, leukocytes, and phagocytes [81, 82, 86].

Cancers can also arise from sites of chronic irritation, infection, and inflammation [84, 85]. Chronic inflammation is related to almost 20% of human cancers [88, 89]. Tumors perform as wounds that fail to heal. Chronic inflammation poses the threat of DNA damage becoming a risk factor for cancer [86]. A normal cell subjected to frequent DNA impairment during chronic inflammation may experience carcinogenesis becoming a tumor cell [82, 84-86]. Patients with Ulcerative Colitis face a 5 to 7-folds greater risk of developing colon cancer. The risk extends to 20-35% as the UC persists for 35-40 years [88, 90, 91]. Inflammatory bowel disease (IBD) is also described as a risk factor for colon cancer [92]. Furthermore, studies have demonstrated that long term use of conventional anti-inflammatory agents can limit the cancer incidence [79, 83, 93-96].

**Inflammatory pathways:** The mechanism of inflammation involves eicosanoids, the arachidonic acid derived lipidic mediators [97]. Arachidonic acid metabolism pathways include cyclooxygenase (COX) and 5-lipoxygenase (5-LO) pathways. Cyclooxygenase pathway is controlled by the COX enzyme which exists in two isoforms, the constitutive form (COX-1) and the inducible form (COX-2) [73]. COX-1 is involved in mucosal protection, platelet activity maintenance, and renal perfusion. While COX-2 is involved in cell proliferation and inflammation is upregulated by growth factors and cytokines [72, 73, 98, 99]. Prostanoid forming cells orchestrate the breakdown of arachidonic acid into prostaglandins (PGs) and/or thromboxanes (TX) in a cell specific complex fashion producing only the desired product [72, 73, 100]. Lipoxygenase pathway involves 5-Lipooxygenase (5-LO) enzyme breaking down the arachidonic acid into leukotriene (LT) and lipoxins (LX) [97, 101, 102]. LTs have remarkable chemotactic activity for recruiting inflammatory components and also release inflammatory mediators promoting inflammation [97, 103, 104]. LTs also have a strong prognosis in asthma, allergic rhinitis, hypertension, arthritis, psoriasis, and atopic dermatitis, atherosclerosis, chronic obstructive pulmonary disease, liver fibrosis, inflammation, cirrhosis and cancer [101, 105-110].

**Anti-inflammatory agents in cancer prevention and treatment:** Anti-inflammatory agents such as non-steroidal anti-inflammatory drugs (NSAIDs) and anti-leukotrienes play an important role in the prevention and treatment of cancer.

NSAIDs and cancer: The main target of NSAIDs is cyclooxygenase (COX) enzyme [97]. COX inhibitors are classified in three different classes, non-selective COX inhibitors (Ibuprofen, diclofenac, naproxen, and ketoprofen), selective COX-2 inhibitors (Rofecoxib, etoricoxib, lumiracoxib, valdecoxib, celecoxib) and partially selective COX inhibitors (Etodolac, nabumetone, and meloxicam) [95, 111-114]. Research has shown the enhanced expression of COX-2 is responsible for inflammatory response and its selective inhibition avoids the unwanted inhibition of COX-1, the isoform involved in housekeeping homeostatic and physiological functions [73, 94, 95, 115, 116].

COX-2 inhibitors and cancer: Evidence suggests that long term use of NSAIDs such as aspirin, sulindac, piroxicam, indomethacin, ketoprofen, and ibuprofen counteract the development of colon cancer [95, 96, 116, 117]. It is now well established that selective COX-2 inhibitors not only reduce the incidence
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Table 2. Reported combinations of COX-2 inhibitor with anticancer drugs and their effects (125-134)

<table>
<thead>
<tr>
<th>COX-2 inhibitor</th>
<th>Combination with anticancer drug</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celecoxib</td>
<td>Cisplatin</td>
<td>Synergistic effect for lung cancer</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>5-FU</td>
<td>Synergistic effect</td>
</tr>
<tr>
<td></td>
<td>5-FU</td>
<td>Synergistic effect</td>
</tr>
<tr>
<td></td>
<td>5-FU</td>
<td>Synergistic effect</td>
</tr>
<tr>
<td></td>
<td>Doxorubicin</td>
<td>Synergistic effect for lung cancer</td>
</tr>
<tr>
<td></td>
<td>Imatinib</td>
<td>Additive effect</td>
</tr>
<tr>
<td></td>
<td>Docetaxel</td>
<td>Additive effect</td>
</tr>
<tr>
<td></td>
<td>Carboplatin</td>
<td>Synergistic effect for lung cancer</td>
</tr>
<tr>
<td></td>
<td>Sorafenib</td>
<td>Additive effect</td>
</tr>
<tr>
<td></td>
<td>Parataxol</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Transtuzumab</td>
<td>Additive effect</td>
</tr>
<tr>
<td></td>
<td>OSU03012</td>
<td>Antagonistic effect</td>
</tr>
<tr>
<td></td>
<td>Ifosfamide</td>
<td>Synergistic effect for lung cancer</td>
</tr>
<tr>
<td></td>
<td>Busulfan</td>
<td>Additive effect</td>
</tr>
<tr>
<td></td>
<td>Chlormethine</td>
<td>Synergistic effect for lung cancer</td>
</tr>
<tr>
<td></td>
<td>Melphalan</td>
<td>Additive effect</td>
</tr>
<tr>
<td></td>
<td>Cis-Platin</td>
<td>Synergistic effect for lung cancer</td>
</tr>
<tr>
<td>Dichloroacetate (DCA)</td>
<td>Additive effect</td>
<td></td>
</tr>
<tr>
<td>Mitoxantron</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Bleomycins</td>
<td>Antagonistic effect</td>
<td></td>
</tr>
<tr>
<td>Aclarubicin</td>
<td>Synergistic effect for lung cancer</td>
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<tr>
<td>Cisplatin</td>
<td>Synergistic effect for lung cancer</td>
<td></td>
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<tr>
<td>Texans</td>
<td>Additive effect</td>
<td></td>
</tr>
<tr>
<td>Mitomycin</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>Additive effect</td>
<td></td>
</tr>
<tr>
<td>Leucovorin</td>
<td>Antagonistic effect</td>
<td></td>
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<tr>
<td>Docetaxel</td>
<td>Synergistic effect for lung cancer</td>
<td></td>
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<tr>
<td>Doxorubicin</td>
<td>Additive effect</td>
<td></td>
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</table>

Table 2 summarizes the current studies in which authors have used the aforementioned rationale to mitigate the cancerous mass aiming for lesser side effects along with enhanced anti-tumor effects.

COX-1 vs. COX-2 inhibitors: Non-selective traditional NSAIDs are associated with gastrointestinal side effects [111, 112, 135]. The risk being highest with indomethacin, ketoprofen, and piroxicam, intermediate with naproxen and lowest with ibuprofen and diclofenac [114, 136]. These gastrointestinal side effects are associated with the COX-1 inhibition involved in maintaining normal physiologic functions. Selective COX-2 inhibitors emerged as safe alternatives of non-selective NSAIDs because of their selective COX-2 inhibition property having less gastrointestinal toxicity [114, 135]. There is strong evidence that COX-2 expression is upregulated in inflammation as well as in cancer [72, 76, 122]. COX-2 enzyme has a key role in PGs synthesis and vascular endothelial growth factor production (proangiogenic factor) instigating endothelial cell growth, proliferation, migration and angiogenesis [93, 137-139]. Several studies demonstrated that selective COX-2 inhibition can impede cancer development and regress tumor mass highlighting the role of COX-2 in cancer progression [71, 93, 122, 123]. However, selective COX-2 inhibitors were found to increase the cardiovascular risks possibly because of selective COX-2 inhibition disturbing the normal Prostacyclin (PGI$_2$)/Thromboxane balance (TXA$_2$) [113, 135, 136, 140, 141]. The disturbed balance leads to irreversible platelet aggregation in blood vessels, vasoconstriction and smooth muscle proliferation promoting thrombotic events. Increased risk of acute myocardial infarction may offset...
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their benefits over non-selective NSAIDs [73, 113, 141-143].

Recent studies also reported inducible COX-1 isoform in particular cells and constitutive COX-2 isoform of the enzyme in kidney and brain cells implying that the distinction between the two enzymes might not be entirely accurate [73, 144, 145]. Furthermore, researches have also highlighted the possible role of COX-1 enzyme in angiogenesis regulation suggesting that further clarification is required [95, 146].

Anti-leukotrienes and cancer: There is accumulating evidence indicating the upregulation of 5-LOX expression and leukotriene receptors in various forms of human cancers, such as colon, breast, head and neck, lung and prostate cancers [101, 104, 147-149]. Their increased expression is associated with pro-angiogenesis, proliferation of tumor cells and is negatively correlated with patient survival [102, 104, 148]. Moreover, reports demonstrate that inhibition of 5-LOX enzyme activity can induce apoptosis in neoplastic cells leading to regression of tumor masses [101, 147, 150]. However, other studies suggest that specific leukotriene receptor blockers instead of 5-LOX inhibitors should be used. This is because specific leukotriene receptor blockers do not inhibit the biosynthesis of lipoxins, that 5-LOX products displaying pro-resolution effects, inhibition of airway hyperresponsiveness and potent anti-inflammatory activities [102, 150, 151].

Targeted therapy

Escaping reticuloendothelial system (RES)

Various techniques have been used by the researchers to enhance the blood circulation time of drug loaded nanoparticles. Studies reveal that nanoparticles with a lesser diameter (<100 nm) and hydrophilic surfaces are capable of avoiding opsonization, escaping RES and are not taken up by liver, spleen, and lung [152-154]. Various surfactants and polymers e.g. polyvinyl pyrrolidone (PVP) and polyethylene glycol (PEG) have been used successfully to avoid RES, providing stealth properties, decreasing clearance, enhancing the blood circulation time and efficiency of the drug [153-156].

PEG coating (PEGylation) has been used extensively for enhancing blood circulation time [154]. Yet there are evidence that PEGylation is only essential until extravasation. Once the nanoparticle has entered the tissue, PEG coating interferes with nanoparticle-cell interaction and endosomal escape leading to significantly compromised intracellular drug delivery [154]. The downside, being referred to as “PEG dilemma” has been tackled with various alternative strategies. These include the use of alternate polymers (e.g. Polyoxazolines, Poly (amino acids), Polybetaines, N-(2-hydroxypropyl) methacrylamide (HPMA), Polyglycerols and Polysaccharides), conditional removal of PEG effect triggered by cellular cues (pH change, enzymatic stimuli, reductive potential) and external cues (thermal stimuli, ultrasonic stimuli) and biomimetic stealth coating using RBC membrane [157-167].

Targeting through enhanced permeability and retention (EPR) effect

Employing the EPR effect has been a key idea in the passive targeting of tumors over the last two decades [153, 168, 169]. Defective leaky vasculature in tumors due to neo-angiogenesis coupled with faulty and poor lymphatic drainage allows passive targeting of the cancerous cells [168, 170]. Studies have shown that passive targeting enables enhanced penetration of drug carriers into the cancerous mass, increasing the therapeutic effects and reducing the side effects by avoiding off targets [169, 170].

Tumor-specific targeting (active targeting)

Malignant cells show the Warburg effect i.e. they are often in hypoxic condition due to significantly enhanced metabolic and growth rate [171-173]. Cancerous cells are distinct from normal cells and can be identified based on several differences from the normal cells, for instance, lower pH, higher temperature, less differentiation, lacking normal physiologic functions and overexpression of specific cell surface receptors including transferrin, folate, hyaluronan, glucose, vascular endothelial growth factor (VEGF) and aldehyde dehydrogenase (ALDH) receptors [171-182]. Researchers have successfully utilized ligands for these receptors as cancer cell targeting agents, reducing the unwanted side effects, minimizing the dose required and increasing the efficiency of therapy. For instance, VEGF, ALDH, N-acetyl-d-glucosamine (NAG), folate, glucose, and transferrin have been used as cancer cell homing
agents for active targeting of drug loaded nano-carriers [174, 175, 177-182].

**Cancer stem cells**

Recent studies revealed a distinct hierarchy of cancer cells in tumor tissue. Cancer stem cell concept (hypothesis) suggests that not all the tumor cells are equal in cancer [77, 183-185]. Only a small pool of tumor cells known as “Cancer stem cells (CSC’s)” have the exclusive ability to initiate cancers [183, 186]. This is a subpopulation of “Self-sustaining cells” which are self-renewing, multipotent and can develop heterogeneous tumor mass [77, 187]. Sometimes also referred to as “Tumor initiating cells”. “Transit amplifying cells” and “Post mitotic differentiated cells” make the bulk of the tumor. Former are rapidly proliferating cells, and the latter are differentiated cells. Both types of cells originate from tumor initiating cells and have no part in tumor initiation [183, 185]. Importantly, recent evidence suggests that tumor initiators or cancer stem cells are very resilient and exquisitely resistant to conventional therapies (Radio and chemotherapy) and tend to be the “drivers” of local recurrence in tumors and metastatic spread [187, 188]. It has been postulated that, notably, cancer stem cells can escape from conventional treatment protocols by remaining quiescent for extended periods of time [189]. Moreover, these tumor initiating cells have the potential to get activated, proliferate, differentiate, and lead to the establishment of local recurrences in tumors or distant metastases [77, 185, 189].

Due to the presence of specific markers on their surface, stem cells can be identified and separated from the bulk cells in a tumor [186, 190]. For instance, markers such as CD133, CD44 and ALDH (aldehyde dehydrogenase) have been used successfully to recognize highly tumorigenic cancer stem cells in HNSCC [183, 184, 187, 190]. CD44 is a cell surface glycoprotein functioning as a hyaluronic acid receptor and is involved in cell adhesion and migration [191].

**Targeting through neo-angiogenesis and tumor vasculature**

The immediate environment around the cancer stem cells is attributed as ‘Tumor microenvironment’ or ‘Tumor niche’ [77, 189]. The components of tumor niche include non-epithelial stromal cells, vasculature and inflammatory cells [192]. This microenvironment is crucial for growth, proliferation, and migration of cancer stem cells [193]. Therefore, any disruption in the interaction between cancer stem cells and its supportive niche or any damage to this tumor niche itself can limit the growth and proliferation of cancer stem cells [192, 193].

Targeting inflammatory cells and angiogenesis are the two recent approaches being used by the researchers to halt tumor growth [73, 111, 192, 194]. Inflammatory cell targeting has been described earlier in the manuscript. Angiogenesis is the consequence of interactions between various regulatory molecules [151]. These regulatory molecules include angiogenesis stimulators and angiogenesis inhibitors. Angiogenesis in a normal physiological process is self-limited by angio-inhibitory molecules [195-197]. Whereas, the balance between stimulators and inhibitors is disrupted during neo-angiogenesis [151]. This is due to the overproduction of angiogenesis stimulatory factors (VEGF, platelet derived growth factor, basic fibroblast growth factor and matrix metalloproteinases) and diminished expression of angiogenesis inhibitory factors (Thrombospondin-1 and 2, angioatin, endostatin, tissue inhibitors of matrix metalloproteinases and Interferons α, β and γ) [151, 195, 197]. Neo-angiogenesis initiated by tumor cells enables the tumor mass to grow in uncontrolled fashion beyond limits [195, 196]. Extensive research has been done to develop angiogenesis suppressing strategies [97, 194, 198]. Researchers have found a strong link between hastily neo-angiogenesis and enhanced COX-2 expression and vice versa [71, 72, 123]. Studies have also shown that specific vascular targeting agents can not only, successfully halt cancer growth but can also regress the tumor mass [194-198]. In 1999 FDA approved the first anti-angiogenic VEGF targeting drug Avastin® (Bevacizumab) [199]. To date, a lot of new anti-angiogenic drugs have been approved by the FDA for cancer [199]. A brief account has been presented in Table 3.

**Photodynamic therapy (PDT)**

Photodynamic therapy is a minimally invasive, dual selective and clinically approved therapeutic procedure for cancer treatment [200, 201].
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Table 3. List of anti-angiogenic drugs approved by the FDA for the treatment of cancer

<table>
<thead>
<tr>
<th>General Class</th>
<th>Approved Drugs (Brands)</th>
<th>Mechanism of action</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monoclonal Antibody Therapies</td>
<td>Bevacizumab (Avastin®)</td>
<td>Monoclonal antibodies directed against VEGF or VEGFR.</td>
<td>Metastatic colorectal cancer (mCRC), non-small cell lung cancer (NSCLC),</td>
</tr>
<tr>
<td></td>
<td>Genentech</td>
<td></td>
<td>gastroesophageal junction adenocarcinoma, advanced breast cancer (Europe),</td>
</tr>
<tr>
<td></td>
<td>Ramucirumab (Cyramza®)</td>
<td></td>
<td>glioblastoma, metastatic renal cell cancer (RCC), advanced ovarian cancer</td>
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<td></td>
<td>Eli Lilly</td>
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<td>(Europe)</td>
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<td>Small Molecule Tyrosine</td>
<td>Axitinib (Inlyta®),</td>
<td>Tyrosine kinase or multikinase inhibitor that target in</td>
<td>Advanced renal cell carcinoma</td>
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<td>Kinase Inhibitors (TKIs)</td>
<td>Pfizer</td>
<td>general VEGFR-1, -2, -3, TIE2, PDGF, and FGFR, KIT, RET,</td>
<td>Advanced metastatic colorectal cancer (mCRC)</td>
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<td></td>
<td>Cabozantinib (Cometriq®), Exelixis</td>
<td></td>
<td>pancreatic neuroendocrine tumors</td>
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<td>Lenvatinib (Lenvima®),</td>
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<td>Pazopanib (Votrient®)</td>
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<td>GlaxoSmithKline</td>
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<td>Regorafenib (Stivarga®), Bayer</td>
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<td>Sorafenib ( Nexavar®),</td>
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<td>Bayer, Onyx</td>
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<td>Sunitinib (Sutent®),</td>
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<td>Vandetanib (Caprelsa®), AstraZeneca</td>
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<td>Inhibitors of mTOR</td>
<td>Temsirolimus (Torisel®)</td>
<td>Inhibitor of mTOR (mammalian target of rapamycin), part of</td>
<td>Advanced renal cell carcinoma, Relapsed or refractory mantle cell</td>
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<td></td>
<td>Wyeth</td>
<td>the PI3 kinase/AKT pathway involved in tumor cell proliferation and angiogenesis.</td>
<td>lymphoma/Non-Hodgkins Lymphoma (European Union)</td>
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<td>Everolimus (Afinitor®)</td>
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<td>Novartis</td>
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<td>Fusion Protein</td>
<td>Ziv-Aflibercept (ZALTRAP®)</td>
<td>A recombinant fusion protein consisting of VEGF-binding</td>
<td>Metastatic colorectal cancer</td>
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<td>Regeneron/Sanofi</td>
<td>portions from the extracellular domains of human VEGF receptors 1 and 2 fused to the Fc portion of the IgG1.</td>
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<td>Other Antiangiogenic Agents</td>
<td>Interferon alfa (Intron® A and Roferon®), Roche, Schering</td>
<td>The precise mechanisms of action are not fully understood,</td>
<td>Hairy Cell Leukemia, Malignant Melanoma, Follicular Lymphoma, AIDS-Related Kaposis Sarcoma</td>
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<td>Lenalidomide (Revlimid®), Celgene</td>
<td>mixed actions, in general, depending upon the specific drug e.g. endogenous cytokine, possesses</td>
<td>Non-small cell lung cancer (NSCLC)</td>
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<td>Thalidomide (Thalomid®), Celgene</td>
<td>immunitymodulatory, anti-inflammatory, and antiangiogenic properties etc.).</td>
<td>metastatic colorectal cancer</td>
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<td>TAS-102 (Lonsurf®), Taiho</td>
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<td>multiple myeloma</td>
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<td>rhEndostatin (Endostar/Endu-available only in China), Simcere</td>
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<td>Allretinoin (Panretin®)</td>
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The process involves three individually non-toxic components including photosensitizer (PS), specific wavelength radiations (normally in the visible or near infrared region) and oxygen [202, 203]. A combination of these simple components in the specific pattern can exert intricate cytotoxic effects on malignant cells [201]. PDT involves the administration of a photosensitizer into the body followed by tumor irradiation with specific wavelength radiations. The wavelength of the radiations corresponds to the maximum absorption band ($\lambda_{\text{max}}$) of the photosensitizer. Activated photosensitizer transfers this energy to molecular oxygen in its vicinity culminating in highly reactive singlet oxygen species [202, 204, 205]. Such species have a half-life of only 1 ms but can exert cytotoxic effects by reacting with vital biomolecules [201]. Depending upon the dose and nature of photosensitizer used, the oxygen concentration in the tumor, light dose and time interval between administration of PS and irradiation, PDT can exert local antitumor cytotoxic effects, damage tumor vasculature and produce systemic immunity by inducing acute inflammation [200, 206]. Tumor homing ligand grafting enables the targeted PS delivery only to the destination malignant cells or tissue. Irradiation is also spatially directed only to the malignant mass area of the body, making the procedure dual selective [203, 205].

Hematoporphyrin (an endogenous porphyrin) was the first PS for PDT, approved by FDA in 1995 [201]. Several less toxic and more sensitive photosensitizers (PSs) have been developed and approved for PDT in the recent past including Porfimer sodium (Photofrin) (HPD) ($\lambda_{\text{max}} = 630$ nm), 5-aminolevulnic acid (ALA) ($\lambda_{\text{max}} = 635$ nm), ALA esters ($\lambda_{\text{max}} = 635$ nm), Temoporfin (Foscan) m-tetrahydroxyphenylchlorin ($\lambda_{\text{max}} = 652$ nm) and Verteporfin ($\lambda_{\text{max}} = 690$ nm). Several other photosensitizers are under clinical trials [200, 201].

The aging field of PDT has been rejuvenated with the advent of activatable bifunctional photosensitizers [201, 203, 207]. The diverse type of photosensitizers has been studied within the last two decades. Following irradiation, bifunctional PS can show remarkable fluorescence while participating in intersystem crossing (ISC) and producing reactive singlet oxygen species at the same time [203, 207]. Such smarter photosensitizers can serve as theranostics enabling fluorescence imaging as well as photodynamic therapy [203].

Furthermore, the emergence of activatable photosensitizers (aPSs) has augmented the attraction for PDT allowing precise control over the treatment [201, 206]. aPSs remain quiescent even under illumination. They get activated selectively in the tumor milieu under specific conditions [208, 209]. Such tumor associated stimuli include usually lower pH (6.5 to 7.2) as compared to that in normal tissues (7.4), higher glutathione (GSH) concentration, overexpression of specific enzymes and certain receptors, macrophage targeting and inhibition of self quenching in the tumor [208-211]. Not only this, dual responsive aPSs can make PDT even more selective [201, 212]. Dual responsive aPS generates maximum singlet oxygen species only when the two tumor associated stimuli are present. One such aPS system was developed by Lau et al. comprising ferrocene quenchers linked to SiPc core via disulfide and hydrazine linkages. Biothiols and slightly acidic conditions i.e. pH ranging from 4.5 to 6.8 can cleave these linkages respectively. Separation of ferrocene quenchers activates aPSs which then display photo-cytotoxic activity in biothiol rich and slightly acidic tumor microenvironment but not in normal tissues [209].

Such remarkable advancements have improved the efficiency of PDT making it dual selective, bifunctional, dual responsive, minimally invasive and precisely controlled therapy [200-204, 212]. Being associated with minimal systemic effects, decreased morbidity, negligible cytotoxicity for normal tissues, lack of acquired or intrinsic resistance, selective cytotoxicity for malignant cells, prolonged patient survival, early stage tumor cure and improved quality of life, PDT has emerged as a vital mainstream anti-cancer therapy [203, 205-207, 211].

**Hyperthermia**

Hyperthermia (40-45°C for over 30 min) has been applied clinically to regress tumors for the last 20 years [213, 214]. Elevated temperatures (41°-43°C) reduce DNA synthesis and halt respiration in human cells [214]. Further heating to about 45°C results in denaturation of chromosome associated proteins. Hyperthermia can also lead to immune system activation, disruption of the plasma membrane,
autophagy and inflammation leading to tumor cell destruction [215-218]. Hyperthermia using computer controlled, sophisticated heating devices and invasive multi-sensor thermometry, has been applied successfully for the treatment of several cancers including malignant melanoma, cervical cancer, soft tissue sarcoma, bladder cancer and recurrent breast cancer [214, 219, 220].

Cancerous conditions (low pH, hypoxia, altered blood supply and poor nutrition) are associated with resistance development against chemotherapy and radiation therapy. Whereas, the damage due to hyperthermia is more likely and pronounced under these conditions [215]. As hyperthermia affects membrane permeability, it can enhance the drug uptake and improve the efficiency of chemotherapy. Thus, hyperthermia as an adjunct therapy can improve the efficiency of chemotherapy and reduce the resistance development against it [213, 215]. Moreover, hyperthermia treatment after radiation therapy impedes cell recovery from impaired mitosis and sub lethal radiation damage by limiting DNA synthesis. Therefore, the combination of precisely localized hyperthermia with chemotherapy and radiotherapy as an adjunct therapy has been suggested [213, 215].

Despite the availability of precise, computer controlled and sophisticated techniques providing accurate radiation fields and dosimetry, the treatment is limited due to hot spots and damage to normal tissues [214, 215]. Studies suggest a temperature around 43°C for 1 hr. as an optimal thermal dose. Whereas, the average clinical temperatures obtained without affecting normal structures are around (40-41°C) [214, 221]. Furthermore, with the present regional radiofrequency, interstitial and superficial techniques, various cancerous sites are unreachable. Temperature inhomogeneity can also lead to unsatisfactory results [213-215].

Current research is focused on dealing with such limitations of heat therapy. A lot of work has been done to develop and modify hyperthermia treatment planning, a valuable tool for improving loco-regional heating [213, 222]. It improves understanding of hyperthermia treatment not only as stand-alone but also as an adjunct therapy in cancer treatment by providing information about the realized heat distributions [214, 222]. Hyperthermia treatment planning has greatly influenced clinical heating techniques. In the past two decades, various new precise, sophisticated and selective hyperthermia technologies have been developed and optimized for loco-regional heating [213, 216, 223]. These techniques involve dielectric model generation, electromagnetic field calculation techniques (differential techniques, integral equation methods), thermal modeling (continuum models, discrete vasculature models), treatment optimization techniques (SAR-based optimization, temperature-based optimization) [214, 215, 217, 222, 224, 225].

Several dedicated sensitive hyperthermia treatment planning software packages have been developed for loco-regional heating providing temperature, electromagnetic and SAR calculations, phase amplitude optimization, thermal modeling, basic and more advanced thermal simulations, tissue segmentation and treatment optimization [213, 214, 222]. These software packages include HyperPlan, AMC DIVA, SEMCAD X (SPAEG), COMSOL, HFSS and CST STUDIO SUITE [213, 214, 222, 226]. Commercial software packages are improving continuously and adapting to real clinical demands [214].

Cancer vaccination

Cancer immunotherapy and cancer immunoprevention refer to the treatment with vaccines that eliminate existing cancer or prevent the development of new cancer, respectively [227, 228]. Immunity is the consequence of a complex interplay between innate (antigen nonspecific) and acquired or adaptive (antigen specific) immune systems. The immunity established by the immune system has the potential to eliminate cancerous cells [229]. Neoplastic cells arise routinely and are destroyed by the immune system. Cancers develop when the protective mechanisms of the immune system fail because of genetic and epigenetic mutations [228, 230]. T-lymphocytes, capable of distinguishing between normal and cancerous cells, are the key components of anticancer immunity [229]. Cancer cells, driven by oncogenes or DNA mutations, over-express specific antigens or marker peptides [227, 231]. Activated T-cells can reject the tumors by recognizing and destroying major histocompatibility complex (MHC) bound cancer specific epitopes.
mulation of T-lymphocytes is dependent on antigen presenting cells (APCs) that recognize, bind and present cancer specific epitopes to lymphocytes [229, 230]. As cancer cells act as poor APCs, the generation of potent anticancer response depends upon the dendritic cells (DCs) [232]. These are bone marrow derived cells that can identify the cancer antigens and present them to lymphocytes. Extremely efficient, DCs develop a link between innate and adaptive immunity and are designated as “natural adjuvants” or “professional APCs” [229, 232].

Cancer immunotherapy

Cancer immunotherapy attempts to harness the natural antitumor response of the immune system through cancer specific antigens and adjuvants [231]. DCs play a vital role in cancer vaccination acting as stimulators of lymphocytes, the key players in anticancer immunity. Different strategies have been adopted to induce effector T-lymphocytes which leads to tumor regression and generation of memory T-cells avoiding tumor relapse [228, 229].

In one such approach, autologous epitope specific T-lymphocytes are developed and expanded ex-vivo. Then these lymphocytes are rein fused into the patients inducing anticancer response in-vivo [229].

The vaccination approach involves the administration of cancer specific antigens along with immune system adjuvants eliciting T-lymphocytes in-vivo [228-230]. Depending upon the cancer type to be targeted, vaccines consist of either oncogenes or tumor genes (neoepitopic vaccines), with or without adjuvants, such as dendritic cells. Oncogenes refer to the DNA of oncoviruses that are associated with several cancers including liver and cervical cancers [233]. Such vaccines consist of either DNA of oncoviruses or viral antigens (short viral peptide molecules). For instance, HPV (human papillomavirus) vaccines, HAV (hepatitis A virus) and HBV (hepatitis B virus) vaccines have been developed by the researchers [234, 235].

Tumor genes are either shared genes (common to many tumors) or unique genes (Specific to a particular tumor) [233]. Neoepitopic vaccines carry tumor genes and/or the specific antigens overexpressed by cancer cells [231]. Studies demonstrate that short, tumor antigen mRNA of mutated alleles or entire mRNA of cancer cells, loaded in DCs can elicit anticancer immunity [230, 236]. The possible mechanism involves the tumor antigen production from tumor mRNA (translation) in the host cell, followed by APC action leading to T-lymphocyte stimulation against tumor antigens [236].

Cancer is the result of genetic and epigenetic mutations that are of diverse nature and cancerous clones vary from patient to patient [237]. This inter and intra-lesional heterogeneity can render the therapeutic vaccines impractical. Moreover, cancer clones keep on changing composition making therapeutic vaccines ineffective with time [238]. Recently researchers have unveiled the possibility of "individualized cancer immunotherapy" [237]. This technique involves the identification of a complete range of patient specific cancer mutations (mutanome) and cancer related epitopes. Then these antigens are produced, multiplied and associated with adjuvants in-vitro, followed by administration into the body [237, 238]. The individual specific entire repertoire of tumor specific antigens along with adjuvants can stimulate and/or harness the T-lymphocyte mediated anticancer immune response [232]. Tumor heterogeneity and changes in clonal composition can also be dealt with adjusting the patient specific neoplastic vaccine’s composition over time according to the new or altered mutanome [231, 237]. Personalized cancer vaccines target the patient specific genetic aberrations with safety and efficacy, showing the potential to become universally applicable tumor specific agnostic cancer treatment [238].

Cancer immunoprevention

Cancer immunoprevention is an approach to prevent infectious and non-infectious tumors employing the same concept of immunotherapy. It involves the use of antibodies, immunostimulators, and vaccines to kick start the body’s natural immune response [227]. HPV, HAV and HBV vaccines are capable of generating anticancer immune response [234, 235]. Still, the technique is not entirely feasible for application in normal individuals due to the general risks associated with vaccination as well as the likelihood of autoimmune disease development.
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[239]. However, it is suggested that the population subgroups with increased cancer risk e.g. individuals with pre-neoplastic lesions or history of hereditary cancer should be considered as possible candidates of non-infectious tumor immunoprevention [227, 239].

However, to realize anticancer vaccine therapy, various challenges need to be addressed. Selection of best tumor specific antigens and development of appropriate delivery mechanisms need diligent work. Further, the immune suppressive mechanisms in the cancer tissue can render the immunotherapy ineffectual [229, 231]. Cancer immune-evasion strategies involve tumor cell intrinsic (escaping immune recognition and elimination) as well as tumor cell extrinsic mechanisms (immune-suppressive tumor microenvironment creation) [231]. As most of the overexpressed cancer antigens are also expressed by normal cells in a controlled fashion, the risk of developing an autoimmune disease cannot be ruled out and requires keen investigation [227, 238, 239].

Scientists aim to subside these downsides by employing improved techniques. Some of the recent efforts include vaccine design improvements (e.g. single supramolecular peptide conjugate vaccines) and combining cancer vaccines with other anticancer therapies (e.g. vaccines complementing checkpoint strategies, vaccine-chemotherapy combinations, vaccine and adoptive T-cell therapy) [231, 232, 237]. With such advancements, cancer vaccination is becoming the forefront of cancer therapy and their future seems bright.

Future prospects

Chemotherapy has been improving continuously and it seems that in the future it will be more effective, specific stem cells and tumor niche targeted involving less toxic and cheaper natural anticancer adjuvants. Commercial software packages for hyperthermia treatment planning are improving continuously and adapting to real clinical demands aiming for realized and precisely controlled loco-regional heating. It is likely that in the future, with the advent of more selective and less toxic activatable photosensitizers, photodynamic therapy will continue to be employed as a stand-alone modality as well as in combination with other anticancer techniques such as chemotherapy. Personalized cancer vaccines will be further improved to deal with alterations in person specific clonal composition and tumor heterogeneity showing the potential to become universally applicable, patient centric, resistance free and tumor specific treatment. Extensive research is being done to develop cancer prevention techniques. Cancer prevention techniques have already been introduced, for instance, prevention through anti-inflammatory agents and cancer immunoprevention vaccines. Refinements in these approaches will most likely make cancer prevention possible in the future.

Conclusion

The total annual economic impact of cancer is huge and is on the rise. Poor early diagnosis, severe adverse effects, high cost and recurrence are the main problems associated with conventional cancer treatment. Extensive research is being done to explore better prospects or refine the current anti-cancer treatment protocols. Successful improvisations in monoclonal antibody development have paved the path for cancer immunopreventive vaccines. Chemotherapeutic agents in combination with natural bioactive anticancer substances and other anticancer therapies demonstrate pronounced anti-neoplastic effects. Anti-inflammatory agents have shown potential as cancer preventing and debulking agents. Targeting inflammatory cells, cancer stem cells and neoangiogenesis are the recent approaches being used by the researchers to halt tumor growth and minimize relapse. Photodynamic therapy has emerged as dual selective, bifunctional, dual responsive, minimally invasive and precisely controlled therapy. Several dedicated sensitive hyperthermia treatment planning software packages have been developed for loco-regional heating providing temperature, electromagnetic and SAR calculations. Personalized cancer vaccines target the patient specific genetic aberrations with safety and efficacy, showing the potential to become universally applicable tumor specific agnostic cancer treatment. Cancer treatment is improving continuously, and the survival rate has inclined remarkably.

Acknowledgements

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