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Chemotherapy or Immunotherapy: A Search for the Potential Anti-Cancer Treatment Strategies

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Abstract: ***In recent days, emerging treatment strategies to combat cancer has provided a new ray of hope for the patients suffering from cancer. Chemotherapy has immense potential; at the same time, many of them have intense side effects. Whereas, immunotherapy for cancer treatment might be an intrinsic way to treat cancer with minimum side effects, additionally, this have long-term efficacy. Further research is needed to predict, whether immunotherapy prevents cancer through direct killing of cancer cells or through preparing proper immunological microenvironment. In spite all modern treatments; recurrence or relapse of tumor is a big concern, which needs to be addressed through some advanced therapy. There is an emerging idea about manipulating the gut microbiota for cancer prevention/treatment. Efficacy of conventional anticancer therapy is reported to be enhanced in such manipulation, which can show future direction of cancer therapy.***

Keywords: Anti-cancer agents, Chemotherapy, Immunotherapy, Immunomodulation, Gut microbiota manipulation

1. Introduction

Cancer is a multifactorial disorder marked by insensitivity to inhibitory signals, liberation from growth factor dependence, impaired replicative senescence, uncontrolled division, neovascularization, metabolic dysregulation and potential for metastasis culminating in generalized dysfunction which penetrates all levels of tissue architecture. Cancer therapy employs diverse strategies depending on the kind of cancer, location, stage, and degree of metastasis [1–6]. Strategies for tissue-targeted therapy may include surgery and radiotherapy for removal of bulk tumor tissue, targeted chemotherapy and immunotherapy. Systemic therapy is targeted for the residual cells whereas for metastasis, chemotherapy and immunotherapies are the way-out [2, 4, 7–10]. Combination strategies have recently been explored to cooperatively eliminate refractory tumors and achieve optimal clinical benefit. Chemotherapy has been classically associated with immune suppression. Recent advances reveal a more dynamic interaction between chemotherapeutic drugs and the tumor microenvironment where chemotherapy can influence immunogenic clearance, altered antigen-presentation, tumor cell targeting, clearance of immunosuppressive cells and conditioning of the immune system [11–13]. A novel immunomodulation strategy employs the potential modulation of the gut microbiome, made possible by the sensitivity and causal relationship dysbiotic environments share with chemotherapy, radiotherapy, and immunotherapy [14, 15]. In this mini review, we outline the principles of chemo and immunotherapy and elucidate the strategies and mechanisms of immunomodulation through chemotherapy.

2. Chemotherapy: For cancer treatment

Developed by Paul Ehrlich in the early 20th century, chemotherapy is an umbrella term referring to the use of chemicals to inhibit infectious agents or malignant cells with minimal effect on normal host cells. Cytostatic drugs target quickly dividing cancer cells. Mechanistically they may be categorized into alkylating agents, alkaloids, antibiotics, and antimetabolites.

2.1 Alkylating agents

Alkylating agents rank among the earliest drugs used in cancer therapy; which includes nitrosoureas, nitrogen mustards, triazines, alkyl sulfonates, and ethylenimines. Alkylation occurs of the DNA double helix where cross-linking between guanine N-7 of one strand with the other is permanently affected [1]. Cyclophosphamide for example has been used very successfully in various lymphomas, leukemias, multiple myeloma etc. Platinum-containing anticancer agents (cisplatin, carboplatin, oxaliplatin), known as platinum coordination complexes, do not alkylate DNA, but form covalent DNA adducts by covalent bonding of the Platinum atom to the N7 atom of purines. This causes inter and intra strand crosslinking which non specifically disrupt the cell cycle.

Rapidly dividing cells including hematopoietic, reproductive and endothelial are also affected by alkylating agents and associated with serious side effects. Apart from this, their utility is limited by the emergence of drug resistance. Tumors can counter alkylating agents through the elevation of intrinsic glutathione levels, by enhancing DNA repair mechanism and also through the modification of DNA damage signaling; in some instances, altering the expression of multidrug resistance proteins [16]. Expression of MGMT (O6-Methylguanine DNA methyl transferase) can repair DNA errors caused by alkylating agents. Temozolomide for example acts by methylating the O6 of guanine and is cytotoxic. MGMT can remove the methyl group and repair DNA causing resistance. Cisplatin resistance can occur by modulating cellular uptake and up-regulation of drug efflux mechanisms and interaction with proteins like metallothionein and small molecules like glutathione [7].

2.2 Alkaloids

Alkaloids are heterocyclic nitrogen containing secondary metabolites in plants employed as protective mechanisms against predation [2]. It has been reported that around 50% of approved anticancer drugs from 1940 to 2014 originate from natural alkaloids [17]. Mechanistically cancer inhibition in alkaloids involve the modulation of signaling pathways involved in apoptosis through DNA damage, ROS mediated DNA and cell damage, activation of caspases, cell cycle inhibition targeting proliferative signaling mechanisms etc[18]. For example vincristine, a potent alkaloid extracted from the common periwinkle plant arrests cell division in the metaphase stage by inhibiting microtubule assembly.

2.3 Antibiotics

In contrast to those used to control infection, most antibiotics used for cancer therapy target DNA as intercalating agents or by causing DNA damage. Antibiotics used for cancer therapy include anthracyclines, bleomycin, actinomycin D, and mitomycin. For example, doxorubicin, a commonly used anthracycline drug attacks multiple targets including Topoisomerase I and II inhibiting DNA replication and blocking RNA synthesis. It intercalates with DNA affecting altered nucleosome assembly, can generate free radicals and can bind membrane proteins altering their function [8].

Changes in the composition of gut microbiota (dysbiosis) are associated with inflammation, a crucial step in in carcinogenesis. For example *Helicobacter pylori* and Hepatitis C virus infections cause cancer through induction of epithelial injury and inflammation [19]. *Helicobacter hepaticus* can activate NF-kβ-signaling networks in hepatocytes and promote hepatic cancer in C3H/HeN mice models [20]. Significant loss of protective gut microbiome and colonization of pathogenic bacteria may affect inflammation and assist bacterial translocation into neoplastic tissue increasing local inflammatory cytokines production and tumor growth. This process could be aided by exaggerated immune responses by resident immune cells [21]. Excessive and irresponsible use of antibiotics can cause the alteration of the gut microenvironment and the immune system, potentially resulting in reduced immune surveillance and cancer [22].

A novel mechanism of antibiotic action has been identified in their potential to inhibit mitochondrial metabolism as an "off-target" effect. The metabolism of normal stem cells differs from cancer stem cells in that their quiescence demands very low mitochondrial numbers and they primarily depend on glycolysis. In contrast, some cancer stem cells have an elevated mitochondrial activity. The 'endosymbiotic theory of mitochondrial evolution', according to which mitochondria directly evolved from endosymbiotic bacteria prokaryotic protein synthesis explains why certain antibiotics like erythromycin, chloramphenicol and tetracycline interfere with eukaryotic mitochondrial biogenesis. This dichotomy has proved effective in inhibiting cancer stem cell proliferation in 12 cancer cell lines, across 8 different tumor types [23].

2.4 Antimetabolites

Antimetabolites are small molecules that substitute or compete with naturally occurring molecules as substrates for synthetic processes. Once inside the cell, they can undergo enzymatic activation to generate their nucleoside or nucleotide moiety. For example, cytarabine is phosphorylated by deoxycytidine kinase producing cytarabine-5´-triphosphate which when incorporated into DNA exerts its cytotoxic effects. Antimetabolites are often used in synergistic or antagonistic combinations in leukemias and solid tumors [9].

A significant drawback of classical chemotherapeutic strategies is the inherent toxicity from affected normal cells. Selectively, targeting of cancer cells and tumor microenvironment (TME) can be achieved through small molecules and antibodies. Small molecule drugs (≤500Da) may be targeted to cell surfaces ligand-binding receptors or intracellular proteins or even the tumor microenvironment. A plethora of dysregulated molecules involved in cell growth and proliferation are attractive targets. For example, HER2, which belongs to the epidermal growth factor receptor (EGFR) family of RTKs, is over expressed in some breast cancers and in non-small cell lung cancer (NSCLC). EGFR kinase inhibitors gefitinib and erlotinib potently inhibit EGFR in patients with NSCLC and the EGFR/ERBB2 inhibitor lapatinib is indicated in ERBB2 positive breast cancer. Targeted therapies are complicated to execute, as cancer is associated with multiple gene mutations, which vary, not only in different cancers but also among individuals with the same cancer. Furthermore, recurrence of cancer may be caused by acquired resistance through mutation accumulation on the target molecule and diversion to alternative pathways as well as drug related factors [24]. Immunotherapy for the treatment of cancer may be a way out; as it is ruled out the possibility of drug resistance and most importantly, it is an intrinsic way to get-rid-off cancer from the body.

3. Immunotherapy: For cancer treatment

In recent days, immunotherapy came out to be one of the essential components of cancer treatment. Treatment of cancer cells with monoclonal antibodies, immunomodulation through CAR-T-cell therapy and manipulation of the polarization of tumor associated macrophages (TAMs) shows its potency to heal or arrest even advanced stage cancer. Immunological responses in some cases are intrinsic body response, which is governed through some external agents. That is why it can show the long-term beneficial effects than conventional therapies. Now, it is a matter of controversy that up to which extent immunomodulation can affect cancer cells to die. For comprehensive conclusion, ample studies are needed in the relevant field.

3.1 Immunotherapy through monoclonal antibodies

Monoclonal antibodies have been recognized as effective agents for targeted immunotherapy. In cancer, their specificity has allowed us to target several associated physiological mechanisms. Monoclonal antibodies can elicit

tumor antigen specific immune responses. These responses may be actuated by antibody mediated cellular cytotoxicity, cross presentation of tumor antigens, or by triggering the immune network [3]. For example, targeting CD20 on malignant and autoimmune B-lymphocytes by rituximab (anti CD20 Antibody) led to remission in several B-cell lymphomas, as well as certain autoimmune disorders and led to improved survival [25]. Similarly, tumorigenesis may be inhibited by altering the inhibition of components of the innate immune system, which themselves are intimately involved in tumor immunity and whose activity regulate the adaptive immune system. For example targeting CD47 accelerates cancer cell killing by phagocytes, including macrophages and neutrophils [26].

3.1.1 Immunomodulators

Immune checkpoints regulate immune responses in innate and adaptive effector cells of the immune system, leading to activation or suppression. Cancer cells commonly express molecules like CTLA4 and PD1, which incapacitate the adaptive immune system from mounting a response. Suppression of CTLA4 for example by ipilimumab and PD1 by atezolizumab has been utilized as targets in melanoma and bladder cancer respectively [4]. Combination therapies involving multiple targets have been utilized to improve response rates for example in ovarian carcinomas [10].

3.1.2 Synthetic immune niches

Modulation of antibody and immune response present potential for treatment related toxicities. The potential for local immunomodulation is in this context a more attractive alternative to systemic therapies. Localization has been achieved by implantation of engineered biomaterial based scaffolds which mimic the tissue organization of for example lymph nodes, thereby providing a targeted site for interaction and function of effector immune cells [27]. Song *et al* (2019) for example have devised a nanogel which through extended delivery of immunomodulatory drugs can convert a pro tumoral microenvironment to an antitumoral one [28].

3.1.3 Engineered antibodies

Monoclonal antibodies have become the mainstay of cancer immunotherapy in the recent past. Their manipulation has greatly improved the specificity and availability of drugs. Since antibodies have a modular multidomain structure, recombinant DNA technology has enabled improved efficacies over conventional antibody treatment and increased the spectrum of possibilities. Improvement in efficiency is primarily made possible by targeting Fc receptors for IgG (FcγRs) and associated physiological mechanisms including regulating their polymorphisms, cytokine regulation and antibody isotype. Combination therapies combining traditional monoclonal antibodies with agents that manipulate FcγRs or improvement in binding capacity may improve therapeutic potential [3]. Apart from this, advances in protein engineering platforms provided several novel antibody constructs for immunotherapy. Bispecific antibodies, for example, which can recognize and bind 2 different antigens simultaneously, may be used to target 2 ligands on the same cell. They can also be designed to direct immune cells including T cells and NK cells to the proximity of tumor cells. For example, Catumaxomab (anti-EpCAM and anti-CD3) and blinatumomab (anti-CD19 and anti-CD3) bispecific antibodies have been employed in the treatment of malignant ascites and ALL respectively [3].

3.2 Cell mediated immunotherapy

Apart from their humoral functions in the immune system B cells are key players in immune regulation and have antigen-presenting capacity. APC function can be acquired by activated B cells, for example, by CD40L/CD40 signaling. CD40L/CD40 signaling regulates APC costimulatory activity and in turn regulates T-cell function via several mechanisms. For an example, B cells that infiltrate tumors produce antitumor specific antibodies and have APC function. Adoptive transfer of these cells in breast cancer and pulmonary metastatic tumor in animal models has resulted in regression of the tumors. This has also opened up avenues to exploit infiltrating B cells by *ex vivo* expansion or using autophagosomes derived thereof to mount T cell responses [29]. These tumor-derived autophagosomes (DRibble) have been used to successfully prime T cell responses in E.G7-OVA tumors in mice [30].

Apart from modulation of their immune checkpoints, T cells have been central in the immunotherapy paradigm. Function of tumor infiltrating lymphocytes (TILs) have been investigated in several types of cancers [31]. However, this strategy is contingent on the existence of sufficient numbers of active anti-tumor T lymphocytes in the tumor of interest, which is not always the case. This may be attributed to the highly unfavorable tumor microenvironment for T cell growth and expansion, given the arbitrary deposition of ECM, anoxic and acidic nature and lack of essential amino acids for their growth [32]. In many circumstances, uncontrolled immune responses were observed. However, advances in recombinant DNA technology have significantly improved outcomes. E.g., targeting cytokine-inducible SH2-containing protein (Cish), a negative regulator of TCR signaling has shown effective tumor remission in animal models. In addition, TCRs can be genetically modified to encode receptors that recognize cancer-specific antigens ensuring a predictable immune response. Along with TCR, genetically altering cytokine expression can prolong graft survival and promote effector penetration into cancer tissue [33].

Chimeric antigen receptors (CAR) described by Eshhar et al (1989) are recombinant protein molecules that direct lymphocyte response toward malignant cells [34]. CARs are prepared by combining an extracellular antigen-recognition domain of an antibody, an intracellular T-cell-signaling domain, and a transmembrane domain. Generation of second and third generation CARs can led to the additional co-stimulatory molecules (like CD28, 4-1BB, OX40, and/or ICOS) and the ζ chain of the CD3 complex were included in the cassette resulting in improved T cell proliferation, survival, cytokine secretion, and tumor lysis [35]. The inclusion of all essentials for T cell function eliminates the need for MHC based signaling to T cells. This is advantageous given that tumors often employ heavily modified expression of Class I and II MHCs and upregulatenonclassical MHC molecules as strategies for immune evasion. Also, phage display libraries can enhance

antigen affinity. High affinity CARs can drastically improve the potency of cell-based immunotherapies [36].

3.3 Immunomodulation of tumor associated macrophages (TAMs)

Tumor associated macrophages (TAMs) support tumor progression through several mechanisms including repression of T lymphocytes, production of tumor supporting cytokines, enzymes and proteins from different intra-cellular pathways etc. TAMs can enable tumor cell invasion [37], angiogenesis and vasculogenises of the tumor [38], intravasation of tumor cells [39], and promoting survival [40], all of which leads to complete control of TME. TAMs can provide a tolerogenic environment to the metastatic cells due to their anti-inflammatory nature as opposed to the more aggressive or pro-inflammatory macrophages, which are variously responsible for preventing disease progression [41]. Due to these features, TAMs fail to exert their preventive effect on cancer, ultimately leading to the disease progression [42].

TAMs are suitable target for immunomodulation. *In vitro* treatment of TAMs with iron nanoparticles [6] or some bacteria [5] reversed their cytokine secretion profile and can polarize TAMs to pro-inflammatory state. Small molecule inhibitors of CSF-1R, an essential signaling pathway for TAM function can successfully reprogram the TME and TAMs and enhance T-cell-mediated tumor eradication. Focal adhesion kinase (FAK) inhibitors have been shown to decrease MDSCs, TAMs and regulatory T-cells thereby improving the TME [43]. Pixatimod, a novel immunomodulatory small molecule employed in clinical trials is capable of inhibiting the infiltration of TAMs [44]. Macrophage reprogramming has been achieved by Chakraborty *et al* through a secreted glycoprotein Fibulin7 which inhibits angiogenesis and tumor cell proliferation [45].

4. Immunomodulation through Chemotherapy: A perspective for cancer prevention

Traditional chemotherapy is known to interact with cancer cells, destroy them and eventually minimizes the tumor load. However, off-target effects of chemotherapy can cause severe side effects, which stays prominent throughout and decline the quality of life of a cancer survivor. Immunotherapy can overcome such problems, but some constrains still exists. In some cases, immune suppression and immune exclusion sacrifice the quality of the immunotherapy. In many cases, negative regulation is observed when immune-checkpoint inhibitors are used. It can cause autoimmune diseases and even death. Immunotherapy can reduce survival and in most of the cases prognosis of patients become uncertain. Most of the time people with older age cannot accept only immunotherapy for cancer treatment. Immunomodulation through chemotherapy might work for those patients. This model can work in three ways, which is discussed here (Figure 1).

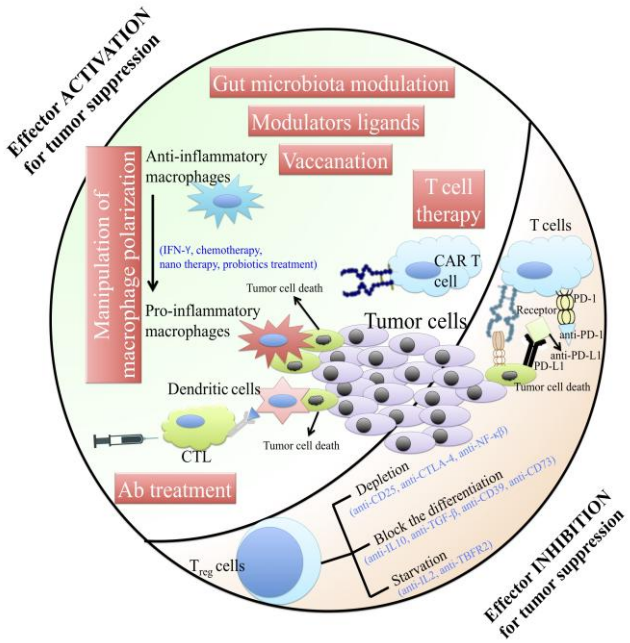

Figure 1: Mechanism of chemo-immunotherapy

4.1 Reconstruction of fresh immune system in tumor tissue

Chemotherapy at high dose can result the depletion of immune system. Transplantation of hematopoietic stem cells needs chemotherapy at high dose, which act as a conditioner to for proper transplantation. In some cases, chemotherapy helps to immune cells to recover faster. For an example, chemotherapy to a patient suffering from breast cancer can help the recurrence of $CD8^+$ T cells faster than $CD4^+$ T cells [11]. Similarly, prolonged chemotherapy recruits considerable amount of T cells at the site of infection to those patients having ovarian cancer [46]. Natural killer (NK) cells play an important role to control cancer progression. After chemotherapy induction, fast reconstruction or recruitment of NK cells is observed to those patients suffering from acute myeloid leukemia [47]. Overall, chemotherapy at high dose creates a platform for the proper execution of immunotherapy. The effectiveness of vaccines and immunotherapies can be enhanced using this preconditioning.

4.2 Eliminate or inhibit the populations which are immunosuppressive

Myeloid derived suppressor cells and regulatory T cells (T_{reg}) are immune regulatory cells, known for their immunosuppressive property. This group of immune cells can reduce intrinsic defense mechanism, which is responsible to cope-up with cancer cells population. Alkylating agents cyclophosphamide or gemcitabine can reduce the number of T_{reg} cells and can suppress the function of those. Low-dose or metronomic cyclophosphamide and gemcitabine have been shown to reduce T_{reg} numbers and their suppressive function [48, 49]. Doxorubicin, 5-fluorouracil and gemcitabine are reported to inhibit the function of myeloid derived suppressor cells [50].

On the contrary, treatment with doxorubicin or cyclophosphamide can increase the number of circulating

myeloid derived suppressor cells in breast cancer patients [12]. In addition, treatment with cyclophosphamide can catalyze the growth of myeloid derived suppressor cells, which is shown in mouse model [51]. Therefore, this treatment strategy might be proven less effective and the drugs, which are used in this purpose sometimes, might affect immune system in such way, which can inhibit anticancer immune responses.

4.3 Manipulation of immune cells

Chemotherapy interacts with immune cells to provide direct or indirect effects. Combination of chemo and immunotherapy can be more beneficial for patients suffering from cancer. If 5-fluorouracil and IFN-α administrated together, an enhanced amount of NK cell population is observed [52]. Moreover, together administration of 5-fluorouracil and cisplatin can increase the infiltration of T cells inside tumor tissues [53]. Patients are at the end-stage of cancer, if treated with cyclophosphamide, the function of NK cells can be enhanced [54]. Activation of $CD8^{+}$T immune cells is observed if cisplatin and paclitaxel are treated at low dose [55]. Inhibitors of microtubule can increase the ratios of $CD8^{+}$ T and T_{reg} cells, and have a positive correlation with the survival rates of cancer patients [56]. Similarly, treatment with taxane or anthracycline can increase the number of effector immune cells inside tumor tissues [57]. Inhibition of tyrosine kinase is plays an important role as it is positively correlated with the survival of patients suffering from gastrointestinal cancer. Tyrosine kinase inhibitor can increase the NK cells and cytotoxic T lymphocytes at the site of infection [13]. Chemotherapy can stimulated dendritic cell population and can indirectly improve T cell functioning at the tumor tissue [58].

5. Conclusions and Future Directions

Cancer is a complex disease. Scientists are dealing with such complexity for more than a century. Recurrence of cancer is another biggest concern in this context which may occur through bystander effect or through semi effective therapy [59, 60]. However, success rate to get rid of this disease is very low. Treatment cost is another barrier, which many patients fail to overcome. Immunotherapeutic potential for cancer treatment has open-up many avenues, but long-term treatment procedure with immunotherapy can decrease the quality of life among the patients. In this context, gut microbiota manipulation to treat cancer came up with a new hope [14, 15]. Human body hosts wide categories of symbiotic microbial communities. Most of them are colonized inside the gastrointestinal tract. The importance of microbiome to control cancer or to react against chemo or immunotherapeutic agents is becoming a new field of research in cancer therapy and hold a great amount of expectations. Nevertheless, lots are yet to be studied and intense research is essential to explore the dark area which then to be translated to the clinic for proper remediation.

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