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Anticancer Chemotherapy Drugs – Magic Bullets or Tragic Bullets: A Search for Real Magic Bullet in Near Sight

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ABSTRACT

The permutation combinations and recombinations of cancer cells gene sequences and the proteomic products expressed epigenetically and the various interactions of cancer cells and their synthetic protein factors in vivo will go a long way in understanding their behavior, in spite of the various insights and information's that have been obtained through research investigations on their genomics and proteomics. The success of chemotherapy in stage I and II cancers in bringing variable percentages of survival and often the failure of chemotherapy in metastatic cases (stage III and IV) drive home the point that every cancer patient shows differential response and every cancer cell or cell groups show differential behavior, unique of it and/or their own, to chemotherapy, respectively. Innovation of a real magic bullet drug against all these kaleidoscopic cancer cells and cancer patients is really a formidable and challenging task to basic and clinical pharmacologic researchers.

Recent research advancement in phytonutrient molecules and the interaction of these molecules with cancer cells in vitro could unravel a real magic bullet to effect cure in cancer patients, *in vivo* fulfilling Paul Ehrlichs words viz., "I trust that we no longer find ourselves lost on a boundless sea but we have already caught a distinct glimpse of the land where we hope, nay which we expect will yield rich treasures for biology and therapeutics."

Keywords: Chemotherapeutic drugs, Antibiotics, Methotrexate

INTRODUCTION

In therapeutic domain, towards malignant cancers, the chemotherapeutic drugs have been employed successfully to kill the cancer cells at their different phases of their growth period. (M-Phase specific drugs; S-Phase specific drugs; cycle non phase specific drugs) [1]. But invariably all chemotherapeutic drugs irrespective of their mechanisms of cytotoxicity and actions produced unbearable side effects to the patients (Prudent Proxies to Prevent Cancer: Personal publication) [2]. Though these drugs administered to cancer patients diagnosed at stage I and II showed promising results of remission and prolonged survival time, the side effects make the patient unbearable. The malignant cells are also not killed completely hundred percent both in radiation and chemotherapy. Post radiation and post chemotherapy window periods are beset with many drawbacks, formidable to the clinical oncologists who encounter challenges besides side effects viz., the kill of normal cells (bystander cells), resistance development in cancer cells mostly in solid tumors to the given drugs and stem cancer cells (0.8-1%) proliferation to reinstate the tumor mass, neoangiogenesis, etc. Recent research publications have revealed still more intricate mechanisms inside the resistant malignant cells which assure their increased rate of survival, consequent to chemotherapy.

ANTICANCER DRUGS

In chemotherapy various cytotoxic drugs and anticancer categories of drugs viz., anti-metabolites, tumour antibiotics, hormones, anti-hormones, vinca alkaloids, and epipodophyllotoxins, cisplatin and several other miscellaneous and new anti-cancer drugs. Pinedo [3] have been employed for treating various types of human cancers. Since cancer cells have acquired and operate several alternative molecular pathways to synthesize various growth

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promoting proteins, cell surface specific tumor antigens or tumor specific surface antigens (TSSA) to which the host immune system shows silence or unresponsiveness; cause suppression of the hosts, general immunity as well as the specific cell mediated immunity, more novel anti-cancer agents are being searched that could target specific molecular pathways or signaling cascades of cancer cells. Despite these drug discoveries, both the initial and acquired drug resistance remains a formidable challenge to the clinical oncologists and resistance mechanisms of cancer cells against drugs are as follows: impaired membrane transport of drugs; enhanced drug metabolism; mutated target proteins; blockage of apoptosis due to mutations in cancer cellular proteins [4].

ANTICANCER DRUGS: PHARMACOLOGIC MECHANISM OF ACTION

Antimetabolites

The therapeutic use of the antimetabolite methotrexate (MTX) revealed its pharmacologic action through binding to the enzyme dihydrofolate reductase in intact cancer cells but its binding is reversible. Moreover the substrate inside the body viz., dihydrofolate compete with MTX, in binding to the enzyme and thus results in the inhibition of reductase enzyme thus impeding the pharmacological action of the drug and necessitating high dosage of MTX which could cause complications in the renal functions of the patient and occasionally the renal toxicity. The alternative approach of new antimetabolite drugs also seemed to have produced no distinct advantage except the suppression of both cell mediated and humoral immunity in man.

Alkylating drugs

In cancer therapy, alkylating drugs have their main focus of action over DNA, involving the most valuable cytotoxic reaction of inter-cross linking thus affecting its replication and further cell proliferation. However it is reported that these drugs exhibit mutagenicity, carcinogenicity, teratogenicity and organ toxicity, etc.

Antitumor antibiotics

These antibiotics exhibit three mechanisms of action against cancer cells viz., DNA intercalation, free radicals activation, and direct effects over the cell membranes. These are considered to be important in cancer treatment, in spite of cellular resistance and organ toxicities.

Vinca alkaloids and epipodophyllotoxins

These alkaloid drugs are well known for the management and treatment of cancers to bind to the micro tubular proteins with high affinity which is their main antitumor action. However studies have revealed that these anti-micro tubular drugs also affect other membrane related functions inside the tissues like hormone secretion, ADH action over renal medulla and cellular resistance, etc. The adverse reactions include neurologic, cardiovascular, mutagenic and teratogenic abnormalities.

Cisplatin

This drug cisplatin and its analogs were the first of the platinum co-ordination complexes to be used as the first anti-cancer agent in man [5]. Though its cytotoxic action over cancer cells have not been deliberated, its anti-tumor effect is related to a selective block to DNA replication resulting from modifications in the DNA templates which is also non-stage specific in the cell cycle [6,7]. Their clinical side effects include the mutagenicity of its cis-isomers, nephrotoxicity, immune suppression, neurologic manifestations, electrolyte disturbances, etc.

Steroid drugs

The steroid drugs are based on the use of hormones in cancer therapy. However the above treatment is largely empirical. Adenocarcinoma of the breast was the first and the most common cancer of the women treated by manipulating the steroid hormone levels. The steroid therapy is classified into: a) ablative type which involves removal of a hormone source (e.g. Ovariectomy) and b) Additive type wherein the hormones are administered to cancer patients. The various steroid hormones used in cancer therapy include:

1. Estrogens (estradiol, ethinyl estradiol, Diethylstilbestrol)
2. Antiestrogens (Tamoxifen, Nafoxidine)
3. Progestins (Hydroxy-progesterone caproate, Medroxy-progesterone acetate)
4. Androgens (Testosterone propionate; fluoxymesterone)
5. Glucocorticoids (Prednisolone, prednisone)
6. These steroidal drugs or their analogs are effective in bringing total cell kills especially in prostate and mammary cancers.

In this context prostate cancers are augmented by androgens while estrogens (anti-androgenic) diminish the tumor; and likewise, the breast cancer is augmented by estrogen but eliminated or markedly reduced by anti-estrogens viz., tamoxifen are of interest to note.

In spite of the beneficial aspects of endocrine therapy, the steroid hormones also produced major untoward side effects. However attempts are in progress to develop steroid linked cytotoxic drugs for minimizing the above side effects and to optimize the therapeutic selectivity in hormone – dependent cancers.

CHEMOTHERAPY – DO WITH OR DO AWAY WITH!

The above outline of information's about the various cancer drugs high light both their merits and demerits. Most of the

side effects noticed in the clinical settings due to chemotherapy were attributed to the following viz.,

1. Most of the chemo drugs are administered intravenously or through oral route. The latent period which these drugs take before targeting the tumor site, may cause some interactions in vivo by enzymes, non-enzymes or analogous substrates, thereby the efficacy of these drugs may not be achieved hundred percent as conceived in pharmacologic-chemistry.
2. Secondly the dosage intensity is another factor for the cause of side effects.
3. Thirdly the frequency of administration, when increased for a single drug regime, it may become a factor. Towards this development of drug resistance due to the consistent usage streptomycin against Mycobacterium tuberculosis has been well documented for several generic drugs.
4. Lastly, the behaviour of cancer cells as well as the normal cells to the administrated drug is yet another important factor. The hair fall and/or loss to chemotherapy drugs is a well-documented evidence/example for their reaction or interaction with the normal hair follicular cells which are also rapidly growing like the cancer cells.

Despite these drawbacks, chemotherapy is still in practice in view of its promising results in regard to prolonged survival period and the overall period of survival and sometimes complete remission of the disease.

Since the time of chemotherapeutic practice, newer drugs and novel methods to increase their target action and efficacy have been attempted. For instance in order to enhance the drug transport and facilitation to the target cancer cells, Burns et al. [8], in as early as 1926 have attempted to modulate the lipid content of the cell membrane and these authors have opined that nutritional manipulation like diets rich in unsaturated fatty acids might facilitate the transport of anti folate drugs. Recently Paulraj [9] in his paper emphasized Budwig diet as a popular alternative cancer therapy.

Similarly, as an alternative to high-dose chemotherapy it was proposed to employ carrier liposomes for the anti-neoplastic drugs in order to facilitate the uptake of the safe level threshold limit of drug dosages by the tumor cells in the early years [10-12].

For some drugs like (e.g. anthracyclins) antitumor antibiotics, the tissue damage is inevitable because these drugs are known to produce free radicals like superoxide, peroxides, etc., and concurrently inhibit the detoxifying enzymes like cytochrome P450. However attempts have been made to decrease the (cardio) organ toxicity and mutagenicity by alternative analogs preparation by alkylating the antibiotic or by replacing the amino group with hydroquinione-quinone functionalities. Similarly cisplatin induced side effects were overcome by the derivation of non-protein bound new platinum derivatives and by appropriate modes of administration. All these attempts implicate the importance of chemotherapy and the novel discovery of drugs to improve further their efficacy and also the immune competency of the cancer patients.

NANOMEDICINE

Very recently the much adored therapeutic tools to eradicate the bacterial populations causing scourgeous diseases as well as the malignant cancer cells are the inorganic metallic oxide nanoparticles. The green (Bio) synthesized metallic nanoparticles are considered more superior to other modes of preparation such as physical and chemical methods regarding such characteristics as:

1. Increased diffusion potential and tissue penetration; inert nature; a good carrier agent; drug delivery and release facilitator; ligand binder and capping/adsorbing substratum and biocompatible size to surpass in vivo reactions if any, etc.
2. Recent research findings also. revealed that the metallic nanoparticles exhibit the magnetic properties even after drug loading and effect the sustained release of the incorporated drugs under in vitro conditions; these studies further revealed that the nanoparticles demonstrated sustained intracellular drug retention relative to drug in solution and dose-dependent anti proliferative effect in breast and prostate cancer cell lines. These NPs can also be easily capped with dose of water insoluble anticancer agents [13].

In view of the above dynamic properties of nanoparticles and their capped phytochemical molecules in interacting with the cancer cells and interfering their proliferating potential through multiple pathways of mechanisms, the combined chemotherapy with nanoparticles coupled phytochemical molecules and the chemo drug may be considered as the future strategy of cancer therapy and they may be the real “Magic Bullets” in near sight. Such magic bullets of chemo drug combined green synthetic metallic nanoparticles are more likely to extend/expand the insights in cancer therapy and will make a paradigm shift in the chemotherapeutic procedures or modalities of treatment towards cure even in metastatic cancers. Such nutrient strategy has been witnessed even in metastatic cancers [14].

The concept of “Magic Bullet” of Paul Ehrlich, i.e., aims the target delivery of anticancer drugs and the disruption of cancer cells with attendant cell death and thereby arresting their multiplication and invasion from their primary site of origin. Towards that the mechanisms of action of inorganic metallic nanoparticles remain paramount, has been elucidated by several studies. Zinc, Copper, Titanium, Gold and Silver Nanoparticles have been employed in several

recent investigations to demonstrate their antimicrobial and anticancer effects both in animal models and cell lines.

Zinc nanoparticles, in one recent study, on their antibacterial activity revealed a lethal effect against *Campylobacter jejuni* even at low temperatures. These Zno Nps induced significant morphological changes, measurable membrane leakage and about 52 fold increase in the oxidative stress-gene expression inside the bacterial cells subsequently resulting in the inhibition of cell growth and eventually their cell death. Gene expression profile studies in *C. jejuni* by Zno also revealed the up regulation of oxidative stress genes [15].

However these metallic nanoparticles particles actions over bacterial pathogens also revealed the latter microbes concurrent in built mechanisms to adapt to the oxidative stress. They synthesize defensive proteins in response to oxidative stress and towards that end several genes that play critical roles in protecting the bacterial cells have been identified. These pathogens synthesize enzymes to eliminate ROS or free radicals. For instance [16]:

1. Their suproxide dismutase (SodB) breaks down O^{-2} to H_2O_2 and O.
2. Their catalase (KatA) inactivates H_2O_2 and interrupts the formation of toxic intermediates.
3. Their alkyl hydro peroxide reductase (AhPC) destroys toxic hydro peroxide intermediates and repairs cellular damages caused by oxidation [17].

In these forms, besides the above specific oxidative stress response proteins, general stress response proteins such as Dank, DraJ, GroES and GroEl, act as molecular chaperons and play a critical role in preventing protein aggregation and refolding which enable the bacterial cell survival as against cell death.

As majority of anticancer drugs as well as radiation therapy exhibit the same mechanism of action, i.e., release of oxidants/free radicals by producing the oxidative stress to kill the cells, the surviving resistant cancer cells give us the cue that their resistant genes/proteins against oxidative stress could have played a critical role in the survival of residual cells subjected to drug action or a chunk of resistant cells and/or the miniscule percent of cancer stem cells (0.8-1 percent) to repopulate the tumor. It is already revealed that cancer cells attain malignancy through gain or loss of gene signatures in both the core and down line genes and by the single nucleotide changes or SNPs [18]. It is of interest to note that when free radicals-generating drugs produce the injurious free radicals in excess, their spill over in the extracellular or circumferential tissue regions after the lysis of cancer cells, the normal cells outside the cancer tissue boundary will be affected and their genetic signatures may promote further cancer cell formation.

In this context, the resistant cancer cells besides recapitulating the embryonic genes functional attributes to de-differentiation, could have recapitulated the prokaryotic characters seems to be of interest and paramount importance in view of the evolutionary descent of cell lineage in eukaryotes.

Hence the anticancer chemotherapeutic procedure and drugs must be endowed with the following goals:

1. They will be specific in selectively targeting the tumor site and cancer cells with more diffusion potentials
2. The drugs should be specifically non-toxic and non-interfering to normal cells.
3. The drugs should be endowed with some in vivo mechanisms other than free radical generating and/or oxidative stress inducing ones.
4. The drugs also selectively upregulated only the apoptotic genes and not the stress response genes (both specific and general).

Until the time such drugs to come in the pipeline, the clinical notion that any kind of/or any number drugs which could increase the level of oxidative stress inside the cancer cells is a good candidate of anticancer agent seems to be untenable, and are to be called only “Tragic bullets”.

REAL MAGIC BULLETS

This is no second opinion about the therapeutic success of chemotherapy as it saved several thousand immune competent cancer patients. The problem lies only in the immune incompetent cancer patients. The real magic bullets of Ehrlich have only to cure these immune incompetent persons.

Towards this the discontinuous drug regimes practiced as of now, leaving some window period seems to be a good augury and represents an important phase/period for providing necessary nutrient supplements to the immuno-incompetent patients towards attaining immune competency. Such an approach is a feasibility considering the anticancer potential and immune stimulating potentials of phytochemical nutrients.

Green synthesized metallic nanoparticles using plant extracts seem to act in different ways. Apart from ROS generations the nanoparticles with their capped phytochemical molecules, their oxidant factors and their subsequent interactions with cancer cells bring the following deleterious effects to cancer cells, viz., the membrane damage due to absorption of nanoparticles to the cancer cell surface leading to cell injury.

The surface defects in the nanoparticles symmetry can also contribute to the cell injury. The bioactive phenolic groups in phytonutrient molecules adhered to the nanoparticles may enhance the anti-microbial potency. Recently Ramalingam

[19] also cited the interaction of phenolic and polyphenolic substances like the isoflavones and the catechins in interfering the glucose metabolism inside the cancer cells and thereby making constraints to their proliferation and by potentiating the patient's immunity through protecting vitamin C *in vivo*.

In this context, various bio molecules demonstrated to prevent the cell cycle of cancers through their interference with DNA synthesis and micro tubular protein synthesis include phytohemoagglutinins, animal lectins, gamma interferons, tumor necrosis factor, defensive proteins, monoclonal antibodies, etc. [20].

FUTILE BIOMOLECULES IN CANCER THERAPEUTICS

In cancer therapy serum antibodies/antisera are of limited value only. The concept of immune conjugates was propounded in yester years to target the metastatic cancer cells migrated to other areas. Four major categories of immunoconjugates comprise: 1. Immunotoxins. 2. Low molecular weight drugs. 3. Biological response modifiers (BRMs) and 4. Radionuclecides. In the first instance toxins of microbial and plant origin such as diphtheria toxin, Ricin gelonin and poke weed antiviral proteins (PAP) are coupled to monoclonal antibodies in order to effect the cytotoxic cell death of cancer cells.

In the second instance low molecular weight drugs such as methotrexate and Adriamycin are conjugated to the antibody molecules. In the third category of BRM, natural immunomodulators or their synthetic analogs coupled to Igs (Mabs) may exert their antitumor effect by activating or directing the biological effector systems. The fourth group of immunoconjugates consists of a radionuclide coupled to an Ig to bring cell death through the radiation. All the above mentioned biomolecules have been discontinued in search of novel anticancer agents.

In cancer prevention nutrition viz., various types of foods, vegetables, fruits, seed containing innumerable phytochemical molecules such as the carotenoids, phenols, poly phenols, mono phenols, saponins, steroids, terpenes (Di-Tri) are of importance in building the immunity of a person and conferring immune competence have been evaluated.

In cancer therapy, novel nanomedicine with carrier nanoparticles adjuvant with chemo drugs and or phytochemical molecules definitely proves to be the future real magic bullets in their own right.

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