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Reasoning of Snake Venom Components as Anticancer Agents

Ramalingam K[1], Paulraj S[2], Babu K[3], Arul vasu C[4] and Kalaiarasan V[5]*

[1]*Senior Project Scientist, India*

[2]*IFS Retd, Executive Chairman, India*

[3]*Assistant Professor, Dept. of Zoology, Arignar Anna Government Arts College, Namakkal, India*

[4]*Professor, Department of Zoology, University of Madras, India*

[5]*Director, Research and Development, India*

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Corresponding author: Ramalingam K, Senior Project Scientist, Snake Park, Chennai, Tamil Nadu, India

Abstract

Though snake venom in anticancer therapy is a conjecture without strong clinical evidence, studies on the various components of snake venom and their properties and/or functions reveal the fact that they can be employed against an incipient or growing or against a fully grown tumor exhibiting metastatic properties. Few preliminary investigations carried out in the line also proves the above contention as tenable.

Keywords: Chemo therapy and Radiation; Snake venoms; Dis-integrins; Allergooncology and Antibiotics

Abbreviations: L-AAO: L-Amino Acid Oxidases; NSAID: Non-Steroidal Anti-Inflammatory Drugs; BRAF: Raf Proto-Oncogene serine/Threonine Kinase; COX II: Cyclooxygenases; EFAs: Essential Fatty Acids; DCs: Dendritic Cells; ILC2: Innate Lymphoid Cells; TFH: Follicular T Helper cells

Opinion

According to the World Health Organization, [WHO]'s Geneva estimate over the next 20 years from now onwards the new case of incidence of Cancer in human will escalate to more than 25 million per year. Jane Mclelland [1] opines that fighting cancer and curing the disease is a matter of knowledge and mustering all resources. In this context the components of snake venom seem to be good anticancer agents to be employed before as well as after metastasis of the disease. Recent investigations have revealed that snake venom, irrespective of its types such as hemotoxin and/or neurotoxin is composed of various ingredients like proteins, peptides, enzymes, non-enzymes, cell dis-integrins etc. to be employed in clinical medicine against cancer.

The various attributes that favor importance and application as anticancer agents are as follows. The peptides like dis-integrins maybe employed to disassemble and destroy the stromal or matrix cells that encircle the tumor mass. The L-AAO of the snake venom maybe employed to increase the permeability of the cancer cell membranes, thus facilitating the entry of chemotherapy drugs. The same may also alter the mitochondrial membrane permeability and enable the exit of Ca_+ +ions into the cytoplasm of cancer cells and promotion of the apoptotic death.

The snake venoms dis-integrins when employed before metastasis could increase the target action of drugs and facilitate their sustained release by destroying the tumor matrix. The same dis-integrins when employed after stage II that is during metastasis about to begin, can inhibit angiogenesis and migration of the cancer cells [2-4]. Even after metastasis the snake venom peptides may be used as chaperones alongside chemo-drugs in view of the venoms potential of diffusion to different organs in conjunction with the organotropisms of the metastatic cancer cells to different organs in-vivo.

In anti-cancer drug response effective penetration and presence of the drug in sufficient concentration at the site of its action is one of the determinants which is paramount. Cancer cells may not be destroyed in chemotherapy even if they are very sensitive, where as they do not have a good supply of blood

to the site (primary) [5]. The drug concentration should be high enough not to allow the cancer cells invasion. For this reason, only intrathecal use of drugs is in vogue in order to cause remission maintenance. But this may also be endowed with immune-suppression. Snake venom studies have revealed that the MMP component is responsible for tissue lesion and that snake venom especially the viper venom in dilute concentration takes one to two minutes to reach blood circulation and for extravasation. This gives a cue that diluted venom complex with drugs and chaperone agents like a lipid vesicle may have quick dissemination to the primary cancer site.

Snake venom may also be combined with non-onco-generic drugs of the metabolic therapy to exacerbate the cytotoxic killing of cancer cells. In this context, several generic drugs like NSAIDs statins, Asprins, Hydroxychloroquin, Doxycyclins, anti-helminthic drugs etc. have been demonstrated to enhance chemo drugs actions on cancer cell death.

The various mechanisms of diverse chemotherapeutic drugs involve the inhibition of cancer cell signaling pathways, hindrance to the replication of DNA. i.e by alkylating the nucleophilic or sequential alkylation, formation of cross links between DNA strands (complementary), prevention of microtubules assembly or blocking their polymerization, Inhibition of onco-proteins synthesis, Inhibition of nucleic acid synthesis. In spite of the above well correlated mechanisms of cancer growth inhibition by these drugs the recurrence of cancers after remission is not uncommon. The drawbacks in chemotherapy may be attributed to the following.

i. The so-called target therapy by chemotherapeutic drugs do kill the malignant cells in a tumor up to 85 percent but leave the resistant cells, cancer stem cells fibroblasts untouched [5].

ii. Most of the cytotoxic chemo drugs work on the principle of free radicals induced cell deaths. This is a drawback since excess free radicals could leave some residual free radicals in the tumor area and they can spill out and damage the normal bystander cells [6].

iii. In the intravenous injection of chemotherapeutic drugs like cisplatin, metho-texrate the infusion is made acidic by the addition of some drugs in order to accentuate cytotoxic action. Therefore, the acidic milieu interior that prevails in the tumor area will enable the survival and replication cum growth by multiplication of the chemo-resistant and radiation resistant malignant cells and the stem cells as well as the conversion or transformation of stromal fibroblast cells into malignant cells [7,8].

Hence the clinical approach in conventional strategies still remains halfway because they cannot bring 100 percent death in the cancer cells. Towards this exploitation of snake venom components as adjuvants and also the employment of generic drugs with pleiotropic effects alongside chemo drugs may be expected to bring the above outcome of 100% kills at the cancer cells. The generic antibiotics which are in usage to cancer therapy include Actinomycin D, Adriamycin, Daunorubicin, Mithramycin, Mitomycin, Bleomycin. All these antibiotics in current application act at molecular level either directly or indirectly with DNA and Protein synthesis in cancer cells. Some anti-cancer drugs are derived from plant origin. All chemo therapeutic drugs are employed against a wide variety of cancers such as Breast adenocarcinoma, Bone sarcoma, Bladder carcinoma, Testicular cancer, Thyroid cancer, Malignant lymphoma, Leukemia, Renal cancer, Ovarian adenocarcinoma, Colorectal cancers, Multiple myeloma, Head and Neck cancer, Prostate cancer, Lung, and Pancreatic cancers etc. Some drugs are myelo suppressive and immuno suppressive in action. Some drugs are mutagenic and carcinogenic. Some cancers develop different type of cancer in other organ system [9]. For instance, the breast cancers during chemotherapy can produce uterus cancer or blood cancer [10].

The so-called targeted therapy of multifarious chemo drugs has also been reported with risk factors. The Vemurafenib (Zelboraf®) and dabrafenib (Tafinlar®) are used to specifically target the BRAF protein to treat melanoma however this drug has high risk of causing squamous cell carcinomas. Since single goal of selective toxicity and kicking of cancer cells during treatment has lack of action over there of peripheral mechanisms operating in -vivo [11].

For instance, the COX-II enzyme action prostaglandins synthesis estrogen dominance, growth factors from without sugar and cholesterol metabolites, EFAs of 6N category, estrogen combined prolactin stimulation other sex hormones are some of the extraneous substances which act as peripheral stimulations and activators of cancers [12,13]. "Allergooncology" is the field that deals with immune inhibitor combined extraneous cancer destroyers are of interest in future studies of toxins like venoms. The immune cells can act as either inhibitors (macrophages 'M1', dendritic cells (DCs), innate lymphoid cells (ILC2), NK cells, Th1, follicular T helper cells (TFH), TCD8+, B lymphocytes, and eosinophils) or favoring the carcinogenesis through tolerogenic cells such as macrophages 'M2,' tolerogenic DCs, ILC3, T, and B regulatory lymphocytes [14]. Several studies have proven the snake venom and its association with the above-mentioned few immune cells favor the inhibition of carcinogenesis [15]. As for as cancer chemotherapy the objective response in patients is more than subjective response of improvement. Several phytochemical secondary metabolites are of immense value in enhancing the subjective response of improvement in the cancer patients. Paulraj [16] in his personal publication on alternative strategies to cancer has thrown more light on the anti-cancer effects of herbal compounds after a thorough perusal of more than thousand research papers and reviews.

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In the orthodoxic treatment surgery and radiation have been annexed with chemotherapy for bringing remission and prolonging the total period of survival, combination of two or more chemotherapeutic drugs demonstrated quick relief and resistance free survival as compared to single agent chemotherapy [17,18].

Conclusion

Even after half a century period of Cancer therapeutic research since 1973 the war against cancer faced sporadic failures and formidable challenges still remain in vogue in clinical oncology due to lack of complete understanding in Cancer biology and the meaningless opposition and discouragement to alternate therapies which proved beyond doubt in their own right and alleviated the various bottlenecks in orthodoxic treatments and allows the patients, immune system to recover and encourage the immunocompetence.

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