IJNRD.ORG ISSN : 2456-4184
INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD) | IJNRD.ORG
An International Open Access, Peer-reviewed, Refereed Journal

REVIEW ON PATHOGENESIS OF HEPATOCELLULAR CARCINOMA BASED ON SHAT KRIYA KALA MODEL-

Dr Fareeda Begum Shaikh[1] Dr Vindhya keshav[2]

1]Professor and guide, Department of PG studies in Kaya Chikitsa, Taranath Government Ayurvedic Medical College and hospital, Ballari

2] 3rd year PG scholar, Department of PG studies in Kaya Chikitsa, Taranath Government Ayurvedic Medical College and hospital, Ballari

ABSTRACT-

In normal healthy cells, there is a balance between tumor oncogenes and suppressor genes. When oncogenes are mutated or overexpressed and tumor suppressor genes are mutated or inactivated, cells grow uncontrollably leading to malignant tumor formation. Cancer formation involves three major steps, initiation, promotion and progression. Kriya kala is the progression of tumor from a single dysplastic foci into highly malignant lesion which is graded from sanchaya avastha to bheda avastha. This knowledge of tumor progression, helps to detect the tumor in very early stages through unmanifested signs and symptoms. In kriya kala model, sanchaya Avastha denotes changes in the single heapatocyte. Prakopa avastha is the conversion of dysplastic foci into malignant lesions. Prasara Avastha denotes metastasis, where the cells breakaway from main tumor cells with the help of vata and enter into blood stream (raktavaha srotas) and lymphatic system (rasavaha srotas). Microvascular invasion, lymph node involvement and extra hepatic spread is considered as sthana samshraya Avastha. Complete manifestation of signs and symptoms is vyakta Avastha. Bheda avastha represents end stage disease with severe impairment in Quality Of Life and severe liver dysfunction. This multi stage approach taken by Ayurveda provides a lot of information about pathogenesis, diagnosis and treatment of cancer in its early stages under the concept of Shatkriyakala. Hence scientific validation of this model is necessary. Details will be presented in full text.

Keywords- Hepatocellular Carcinoma, kriyakala, dysplastic foci, malignant lesion

FULL ARTICLE-

INTRODUCTION-

Nearly all cancers arise from a single cell. The clonal origin is the discriminating feature between neoplasia and hyperplasia. Multiple cumulative nutritional events through a series of steps from normal, initiated and pre neoplastic to premalignant and finally to highly malignant neoplasm accounts for the progression from normal to malignant phenotype. The three major steps involved in the cancer process are initiation, promotion and tumor progression. Kriya kala in the progression of tumor from a single dysplastic foci into a highly malignant lesion through its metastasis to portal veins is graded from sanchaya avastha to bheda avastha. The knowledge of kriya kala helps to understand progression of tumor which inturn helps to detect the tumor and retard the progression in the very early stages through unsaid signs and symptoms of the diseased person. Kriya kala holds a scientific base to prevent mutation of gene which is a major hallmark for cancer initiation.

MATERIALS AND METHODS-

The objective of the study is to understand the pathogenesis of Heparocellular Carcinoma based on shat kriya kala model.

KRIYA KALA MODEL-

SANCHAYA AVASTHA AND HEPATOCELLULAR CARCINOMA-

During sanchaya stage, one or more doshas undergo slight increase in their chief site. Vata in pakwashaya, pitta in amashaya and nabhi and kapha in uras. This accumulation produces mild symptoms like stabda and poorna kosta if vata dusti occurs, peetavabhasata and mandoshmata in pitta dusti and anga gourava and aalasya in kapha dusti and also represents in the form of iccha and dwesha for certain foods, activities[1] etc..liking or desire for those which possess qualities opposite to those of the increased dosha and dislike or aversion for those which caused the increase of the dosha. If the person recognizes these instincts and acts accordingly, the doshas will come back to their normal condition. On the other hand, if they are not recognized and the person continues to indulge in unhealthy foods etc..the doshas undergo increase further.

In Hepatocellular Carcinoma, change in the single hepatocyte refers to sanchaya Avastha. Modification in DNA structure like inversion, addition, deletion etc are happening in this stage. Hepatic cell mutation due to its own direct and indirect causes refers to early pathognomic stage. Fatty liver, hepatitis, cirrhosis are having their own sanchayadi avasthas. But in HCC, these are sanchaya Avastha leading to dysplastic foci [less than 1 mm] or dysplastic nodules [greater than 1 mm] which are considered as precancerous and this entire concept can be considered as Prathama kriya kala for HCC. The causes for the vide about sequelae are many. Chronic infection by HBV or HCV, alcohol abuse, metabolic syndrome [Diabetes and Obesity], Non Alcoholic Steatohepatitis, Hemochromatosis [associated with HFE1 gene germ like mutations], Alpha 1 Antitrypsin deficiency, Autoimmune Hepatitis, Wilsons disease, Cholestatic liver disorders, family history of HCC,

tobacco chewing and aflatoxin B containing products induces TP53 mutations and adeno associated virus is associated with HCC in individuals.

PRAKOPA AVASTHA AND HEPATOCELLULAR CARCINOMA-

In prakopa stage, doshas increase further and spread to many of their own sites elsewhere in the body in addition to the chief site and exhibit their own specific symptoms in all places. These are morderate in nature, the person feels that he is not well but still goes about his daily routine. In prakopa stage, vata dusti lakshanas like kosta toda and sancharana, pitta dusti lakshanas like amlika, pipasa and paridaha and kapha dusti lakshanas like annadwesha and hridayotkleda are experienced by the subject[2]. Continued exposure to carcinogens leads to conversion of dysplastic foci into malignant lesions. This is the progression stage of cancer which is the ability of a compound to induce an area of proliferation in initiated tissue and stimulate tumor formation. The main stages in the development of the dysplastic foci follows a self sufficiency in growth signals where cancer cells produce abnormal amount of growth factors [autocrine stimulation] or may stimulate neighbouring cells to produce growth factors [paracrine stimulation]. Insensitivity to anti growth signals through various mechanisms including loss of endogenous expression, loss of autocrine activity and disabling of anti growth signalling forms a major pathway in development of dysplastic foci. Evasion of apoptosis, cell survival and immortality by rejoining of telomeres, sustained angiogenesis and immune invasion. Regulatory T cells are a subset of CD4+ T cells that suppress effector CD8 T cells thus playing an important negative role in antitumor immunity. Several studies have shown that HCC tumor tissues appear to be infiltrated with Tregs and also that subjects with HCC have an increased number of circulating Tregs thus implying that they likely play a pathogenic role in HCC. Another mechanism of immune suppression in the tumor microenvironment is an increase in immunosuppressive cytokines such as in IL4, IL5, IL8 and IL 10 with simultaneous suppression of immune activating cytokines IL 1, TNF and interferon gamma. This unique cytokine signature has been shown to promote tumor metastases in future and circulating levels of IL10 were reported to be associated with poor prognosis. Cancer cells exhibit metabolic aberrations that enable them to tolerate suboptimal conditions. For example, hypoxia, lack of nutrients, acidic tumor microenvironment, intracellular perturbations associated with accelerated proliferation. Metabolic shift to aerobic glycolysis is a common hallmark of highly malignant tumors. Increased uptake of glucose and gluatamine are typical metabolic characteristics of cancers. These dysplastic foci with the above said mechanisms modifies themselves into a metaplastic nodules which is considered in prakopa stage of HCC. According to Child pugh scoring, this prakopa stage describes very early stage single nodule less than 2cms in the hepatic area.

PRASARA AVASTHA AND HEPATOCELLULAR CARCINOMA-

Prasara is a stage of spreading. In prakopa stage, the doshas which have remained in place so far, becomes ready to move. in prasara stage, the Doshas overflow and spread or move to other areas or organs of the body. Vata prasara lakshanas like vayu vimargagamana and atopa, pitta prasara lakshnas like osha, chosha, paridaha and dhumayana and kapha prasara lakshanas like arochaka, avipaka, angasada and chardi are seen[3]. Metastasis, where the cells breakaway from main tumor cells with the help of vata and enter into blood stream (raktavaha

srotas) and lymphatic system (rasavaha srotas) can be considered in prasara avastha. Vata Dosha is the major culprint in moving Pitta, Kapha, Dhatus and Malas to other places. Thus, it appears that the vata is a key factor that mediates the Prasara stage in the cancer manifestation process. In this stage, the vitiated Doshas continuously spread outside of their normal sites. According to child pugh scoring, early stage [A] describes 1 HCC or 3 nodules less than 3cms, intermediate stage [B] which describes multinodular HCC and advanced stage [c] indicates portal invasion that is metastasis to the portal veins.

STHANA SAMSHRAYA AVASTHA AND HEPATOCELLULAR CARCINOMA-

Sthanasamsraya or the settlement of doshas at a particular place occurs when vitiated Doshas are circulating and settle in areas of srotavaigunya[4].These weak or defective sites may have tissue depletion or certain disturbances in their normal surface. Furthermore, a specific causative factor may have an affinity towards particular channels or tissues, which leads to a defective site and the manifestation of a disease. All the etiological factors may not be causative for a disease. Every tissue of the body requires its own etiological factor related to particular involved doshas and dushyas (body tissues, i.e., rasa, rakta, mamsa, meda, asthi, majja and shukra). For example- like HPV virus can cause only cervical and breast cancer only. A particular pathogen has a specific affinity towards a particular tissue, where it causes a disease. In such conditions, the union of Doshas/Dushyas at a particular site is called Sthanasamsraya. Vata takes the cells to the different parts of body to the place where there is khavaigunyata. In case of Hepatocellular Carcinoma, there is mainly microvascular invasion [branch, hepatic or portal vein], lymph node involvement and extra hepatic spread. For tumor cells to break loose from a primary mass, enter blood vessels or lymphatics and produce secondary growth at a distant site, they must go through a series of steps. The process of local invasion and distant spread involves passages through barriers before gaining access to the vascular lumen. This includes making the passage by the cancer cells by dissolution of extracellular matrix at 3 levels, firstly, at the basement membrane of tumor itself. Secondly, at the level of interstitial connective tissue and at the basement membrane of microvasculature. The following steps are involved in the process 1) Aggressive clonal proliferation and angiogenesis. The first step in the spread of cancer cells is the development of rapidly proliferating clone of cancer cells. Tumor angiogenesis plays a very significant role in metastasis since the new vessels formed as a part of growing tumor are more vulnerable to invasion because these evolving vessels are directly in contact with cancer cells 2) Tumor cell loosening- Normal cells remain glued to each other due to the presence of cell adhesion molecules, E epithelial- cadherin. In epithelial cancer, there is either loss or inactivation of E Cadherin which results in loosening of cancer cells 3) Tumor cell- extracellular matrix interaction- loosened cancer cells now are attached to extracellular matrix proteins 4) Degradation of extracellular matrix- certain matrix degrading enzymes, metalloproteinases [Collagenases and gelatinase] and other protease, cathepsin D etc.. bring about dissolution of extracellular matrix- firstly basement membrane of tumor itself, then make way through the interstitial matrix, and finally dissolve the membrane of the vessel wall 5) Entry of Tumor Cells into Capillary Lumen- The tumor cells after degrading the hasement membrane are ready to migrate into lumen of capillaries or venules through two category of molecules (1) tumor cells derived motility factor and (2) cleavage products of matrix compounds. After the malignant cells have migrated through the breached

basement membrane, these cells enter the lumen of lymphatic and capillary channels 6) Thrombus Formation- The tumor cells protruding in the lumen of the capillary are now covered with constituents of the circulating blood like platelets, and form the thrombus. This provides nourishment to the tumor cells and also protects them from the immune attack by the circulating host cells. 7) Extravasation of Tumor Cell- Tumor cells in the circulation (capillaries, venules, lymphatics) may mechanically block these vascular channels and attach to vascular endothelium. Here the sequence similar to the local invasion is repeated and the basement membrane is exposed. 8) Survival and Growth of Metastatic Deposit- The extravasated malignant cells on lodgment in the right environment grow further under the influence of growth factors produced by host tissues, tumor cells and by cleavage products of matrix components. Metastatic deposits may further undergo metastasis to the same organ or to other sites by forming emboli.

VYAKTA AVASTHA AND HEPATOCELLULAR CARCINOMA-

Fifth kriyakala is the stage of full manifestation of the disease with all its characteristic symptoms and signs[5]. They vary in number and strength from one subject to another depending upon the age, sex, constitution, strength of the causes and many other factors. The diseases are given specific names based on the chief symptom/sign, the organ affected and many other factors. They are classified as arising from any one of the doshas, two of them together or by all the three of them together. The abnormalities though profound can be brought to normal easily when effective treatment and all other favorable factors are present and with difficulty in the presence of unfavorable factors, the disease becomes uncontrollable and progresses further to the sixth and final stage. Vyakta is the stage where HCC manifests itself completely. The symptoms that appear at this stage are used by medical professionals to examine and diagnose cancer, which helps in developing a treatment plan. Symptoms of HCC include malaise, weight loss, anorexia, abdominal discomfort or signs related to advanced liver dysfunction. In HCC, three parameters are relevant for defining a treatment strategy; tumor status, cancer related symptoms and liver cell dysfunction. Advanced stages where subjects present cancer related symptoms or tumors with microvascular invasion [branch, hepatic or portal vein], lymph node involvement or extra hepatic spread. This advanced stage of cancer is the vyakta Avastha. Five therapies are adopted by guidelines and BCLC classification; surgical resection, liver transplantation, radiofrequency ablation, chemoembolization and systemic therapies like sorafenib, regorafenib, Lenvatinib, cabozantinib, ramucirumab.

BHEDA AVASTHA AND HEPATOCELLULAR CARCINOMA-

Bheda is the final stage where the progression of cancer reaches an end. Complications of cancer will be seen and finally may lead to death[6]. In HCC, bheda avastha represents end stage disease with severe impairment in Quality Of Life and severe liver dysfunction. Incurability of tumor is a complex and multifaceted concept. Tumor-related factors include, advanced tumor stage (e.g., large size, multifocal, vascular invasion), high-grade tumors (poor differentiation), tumor recurrence after treatment, resistance to chemotherapy and targeted therapies. Subject-related factors include, underlying liver disease (e.g., cirrhosis, chronic hepatitis), poor liver function (e.g., Child-Pugh class C), comorbidities (e.g., Diabetes, Hypertension), age and performance status.

Treatment-related factors: Inadequate or delayed treatment, lack of response to initial treatment, tumor progression during or after treatment, development of treatment-resistant clones. Molecular mechanisms include genetic mutations (e.g., TP53, CTNNB1), epigenetic alterations (e.g., DNA methylation), activation of oncogenic pathways (e.g., Wnt/β-catenin), immune evasion mechanisms. Multinodular Hepatocellular Carcinoma with tumor size greater than 3 cms with vascular invasion, high alpha-fetoprotein (AFP) levels are the grave prognostic factors in HCC resulting in incurability where there is lack of response to multiple treatments. Subjects at this stage should be considered for nutritional and psychological support and proper pain management.

DISCUSSION-

The ayurvedic intervention rather than the targeted therapies for destruction of the tumors is beneficial to the improvement of the metabolic defects and restoration of normal tissue functions and increase in QOL of subjects. The holistic approach of ayurveda could become an essential component for cancer treatment by using immunotherapy. Moreover, ayurveda gives insight on the condition of doshas at each stage and can be used to track a disease by measuring Vata, which could be controlled if it falls outside of normal levels. According to Ayurveda, kapha, vata dosha, ama visa, agnimandya appear to be the main morbid factors for cancer. Vata is a key factor for the prasara stage in the cancer manifestation process, which can be only diagnosed with the help of clinical involvement. However, if doshas are at the first stage, a simple line of treatment can prevent the condition from progressing to the next stage in the manifestation of cancer. Ayurveda also has indirect approaches to the treatment of cancers because therapies aim to eliminate vitiated doshas, rejuvenate body functions and restore immunity. This is similar to allopathy clinical approaches which use immunotherapy and cancer vaccines. Ayurvedic treatment regimens are largely designed to restore the body's natural defense mechanisms and self-healing powers. Ayurvedic therapies are used to promote long-term recovery from a disease by strengthening and rejuvenating major body systems. It is obvious that if a disease is diagnosed in a holistic manner, its treatment is also holistic. Moreover, although manifestation and complication are the only phases recognized by allopathy medical science to diagnose or treat cancer, the multi-stage approach taken by Ayurveda provides a lot of information about pathogenesis, diagnosis and treatment of cancer in its early stages under the concept of Shatkriyakala.

CONCLUSION-

This concept of shat kriya kala is applicable but not yet validated scientifically. Hence, the validation of the Shatkriyakala model describing from sanchaya stage to bheda stage, with the help of allopathy sciences which starts with mutation of DNA upto metastasis and end stage disease could be a great achievement in the field of medicine. Hence this study is presented.

REFERENCES-

1] Acharya Sushruta, Sushruta Samhita, Nibandasangraha commentary by Dalhana, Sutra sthana, 21st chapter, verse 18, p103.

2] Acharya Sushruta, Sushruta Samhita, Nibandasangraha commentary by Dalhana, Sutra sthana, 21st chapter, verse 27, p104.

3] Acharya Sushruta, Sushruta Samhita, Nibandasangraha commentary by Dalhana, Sutra sthana, 21st chapter, verse 32, p105.

4] Acharya Sushruta, Sushruta Samhita, Nibandasangraha commentary by Dalhana, Sutra sthana, 21st chapter, verse 33, p105-106.

5] Acharya Sushruta, Sushruta Samhita, Nibandasangraha commentary by Dalhana, Sutra sthana, 21st chapter, verse 34, p106.

6] Acharya Sushruta, Sushruta Samhita, Nibandasangraha commentary by Dalhana, Sutra sthana, 21st chapter, verse 34, p106.