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Case Report

Assessing the Approaches to Chemotherapy Plus Phytohemagglutinin (PHA) Immunotherapy in Advanced Cancers

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Abstract

Background: The indication was that chemotherapy and/or radiotherapy were the major skillful of cancer therapy. Phytohemagglutinin (PHA) stimulate host immune lymphocyte activity, inducing the generation of interleukin-2 and interferons. Moreover, another approach to the traditional medicine also occupied its important advances in this field of treatment. In search for effective strategies of cancer therapeutics, in current study, I had summarized the retrospective study of cancers under remission, with the combination chemotherapy in conjunction with PHA and/or traditional medicine.

Methods: 17 available cancers were entered in combination of chemotherapy and PHA during 1993-97. The mean age at onset was 45.3 years (range 10-72 years). All other benign neoplasias (e.g. thyroid tumors, lipoma, benign breast tumors) were not statistically included in this group.

Results: During the schedule of drug administration, all patients were treated with different dosage of chemotherapy in conjunction with traditional medicine. In 17 cancers, the rate of Complete Remission (CR) was achieved in 6 advanced patients (35.3%). 3 CR patients with advanced cancers was survival over 10 years, the longest cancer 18 years. Two advanced hepatocellular cancers were successfully treated using chemotherapy and cantharidin and/or traditional medicine, each with 30-year survivors. Traditional medicine also showed its benefit in 2 lung cancer,1 thyroid cancer and 1 lymphoma respectively.

Conclusion: In this study, a series of the long follow up of those cured patients with cancers were reported. It was likely experienced that a CR was a pivotal influencing factor in those longest survivors, and traditional medicine was also recommended. PHA was found to indeed the stimulation of lymphocytic kill cell activity, thereby exhibiting its anti-neoplastic activity. In previous study, Induction of neoplasm (thumb size) in thyroid gland of one postoperative patient with breast cancer was conducted by herb seaweed. The putative mechanism of oncogenic transformation in thyroid gland in this patient was that iodine contained seaweed drug was participated the biosynthesis of thyroxine. Over-synthesized thyroxine coupled with its aberrant proto-oncogenic receptor THR (oncogenic Thyroid Hormone Receptor), stimulating the prolonged hyperplasias and metaplasias of thyroid follicular cells in thyroid gland, tumor development.

Keywords: Cancer, Chemotherapy, Target oncogenic receptor, Immune therapy, Traditional medicine

Introduction

Over past decades, chemotherapy is a common use of cancer treatment. Traditional systems of medicine all over the world even traditional medicine and cancer have been using plants and plants products for therapeutic intention. Recent important advances have been increased acceptance in oncology that those patients with disseminated tumors were settled to the chemotherapy with targeting oncogenic receptor [1-32,71-74], and/or adoptive immunotherapy [33-39]. Phytohemagglutinin (PHA), an immune glycoprotein antigen (mitogen) with MW 120, 000, directly stimulate host immune lymphocyte activity, inducing the generation of interleukin-2 and interferons, and initiating DNA synthesis of cells. It was under investigation that PHA is the Growth Factor (GF)-like effect on hematopoietic tissues, and successful therapeutics of those patients with aplastic or hypoplastic anaemia. PHA is otherwise the micro-angiogenesis of bone fracture and regeneration of bone. In current study, I summarized the retrospective analyses of the combination of chemotherapy with PHA in the treatment of advanced cancers.

Methods

Seventeen patients with available advanced cancers were entered in the study during 1993 to 1997. All 17 patients were treated with different dosage of chemotherapy plus PHA at the period of protocol. The mean age at onset was 45.3 years (range 10-72 years), of 13 patients were initially hospitalization. The criteria of Complete Remission (CR), and/or Partial Remission (PR) is according to the rules where physician have in common with in clinics.

Results

All 17 patients were in progression at onset diseases. The response of remission was achieved after one to six courses of treatment including chemotherapy plus PHA and/or traditional medicine. After statistically analyses, all patients obtained response to treatment (CR+PR: 14/17,82.3%, Table 1). Among them, 4/17 were CR, 2/17 were in short CR. One patient with nasopharynx cancer, the diplopia and unable vision in his right eye were once recovered to "normal" visual acuity under the combination chemotherapy of VCMF plus traditional medicine. In this case, PHA, an important cytokine invoking host's immune, mediated substantial regression of his metastatic lymph node. An epidermoid carcinoma with rodent ulcer (8x5cm) was once in response as to an approach of a small dosage of chemotherapy and local application of 5% Fu of retinoic acid (mixed PHA) ointment. A short CR was once achieved by the approach to the combination chemotherapy (VCMF plus PHA regimen) in one of malignant pleural mesothelioma. An advanced lung cancer with much malignant hydrothorax was in CR through a major regimen of traditional medicine with the combination of small dosage of cyclophosphamide and PHA therapy. During the period of treatment ,17 patients except for one case were escaping of severe side effects such as fever, and even capillary-leak syndrome. 1 patient represented neurotoxicity after a series of 5-Fu infusion. During follow up, 9 patients under remission eventually dead without any maintance treatment due to economic difficult problem. A rapid relapse due to the progressive diseases was observed in 3 cases after a short remission (PR and/or CR). An evaluation of 3 long-tern survivors over 10 years was achieved.

Table 1: Patients characteristics.

No	Sex	Age	History of disease	Diagnosis	Protocol	Response	Remission (month)
1	F	54	3yrs	Advanced colon cancer(4x6cm)	5-Fu+PHA (1410mg)	PR	2+
2	F	43	7yrs	Metastatic lung (mastectomy) cancer(3x3cm)	VCMF+PHA (880mg) +DES	PR	10+
3	F	55	8+(months)	Metastatic palatum cancer (soft palatum: 3x5cm, an egg size; right neck lymph:3x4cm)	VCFP+PHA (660mg)	CR	18yrs
4	M	43	3yrs	rectum cancer(3x3cm)	VCF+PHA (570mg)	MR	7+
5	M	58	3yrs	Malignant lymphoma (IVB, fused mass consists of 12 lymph nodes:7x10cm)	VCMF+PHA (110mg)	PR	10+
6	M	38	13yrs	Advanced submaxillary cancer; metastatic lymphoma (fused tumor from submaxillary to left lymph nodes:10x15cm; right neck lymph nodes:3x4,3x3)	VCMF+PHA (880mg)	MR	2yrs
7	M	42	2yrs	Malignant lymphoma (IVB, right neck: fused mass consists of 12 lymph nodes: each 1.5x2- 2x3; left neck: fused mass consists of 8 lymph nodes:1.5x2- 4x5cm)	VCM+PHA (240mg)	MR	4+

8	F	38	6months	Nasopharynx cancer (right neck: 6x5cm)	VCMF+PHA (540mg)	PR	4+
9	M	20	2yrs	Chronic malignant histiocytosis (left neck:6x5cm; right neck:2x3cm; left inguinal:4.5x2.5cm; spleen lower reach to umbilicus)	VCMF+PHA (310mg)	CR	14yrs
10	M	40	3 months	Left lung cancer (4.5x4.9cm, malignant hydrothorax)	CF+PHA (100mg) +TCM	CR	10yrs
11	M	10	3 months	Malignant pleural mesothelioma (malignant hydrothorax)	VCMF+TCM+PHA (870mg)	Short CR	2+
12	M	58	2+months	Malignant lymphoma(8x6cm) tonsillar cancer (a thumb size)	VCMF+PHA (1120mg)	PR	2+
13	M	43	3+months	Nasopharynx cancer (a thumb of metastatic right neck node)	VCMF+PDD+PHA (510mg)	CR	3yrs
14	M	47	1yrs	Nasopharynx cancer	VCF+PHA (340mg)	PR	3yrs
15	F	72	1yr	Epidermoid carcinoma (a 3x5cm rodent ulcer)	5-Fu+PHA (60mg) 5%Fu of retinoic acid ointment	PR	2yrs
16	F	47	2months	Ulcerative gastric cancer	VCMF+Ara-c+H+PHA (160mg)	Short CR	4+
17	M	62	4months 17	Laryngeal cancer	VCMBF+MTX+PHA (90mg)	PR	4+

Note*: VCMF: Vincristine,VCR; cyclophosphamide, CTX; mitomycin C, MMC; 5-fluorouracil,5-Fu; B, bleomycin; H, homoharringtone; PDD, Cisplatin; P, prednisone; TCM: Traditional medicine; MR: Minor response; yrs: years.

Case reports

Case 1: A 54-year-old woman with advanced colon cancer for a period of 3 years. At admission on October 10,1993, she suffered from symptoms of vomiting, right abdominal vision mass with intensive abdominal pain complicated by interestinal obstructive constipation. X-ray and an ultra sound examination consistently showed an ascending colon carcinoma mass of 4x6cm size which was in further confirmed by colonoscope (Figure 1). PR was achieved after one course of 5-Fu (5.5gram) and PHA regimen, with relief symptoms of soft fluid diet even rice gruel. The stools were of normal caliber and consistency. Total dosage of PHA 1410mg.

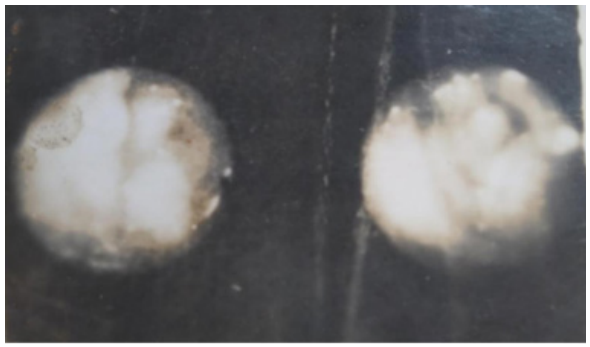

Figure 1(Case 1): An ascending colon cancer under colonscope at diagnosis.

Case 2: A 55-year-old woman was diagnosed as having metastatic palatum cancer on November 6,1993 when she presented with tumors both in her cavity of the mouth and neck lymphadenopathy. On examination revealed 2 lymph nodes (4x3cm) enlargement in her left neck. A 3x5 cm mass was found in her palate molle which was covered over uvula palatina. Moreover, the left side of her face also had a thumb lymph node palpable. Cures were achieved by use of combination chemotherapy (VCR, CTX, 5-Fu, PHA 660mg), and in 18 years follow up she died of relapsed oral cancer.

Case 3: A 43-year-old breast cancer after mastectomy was well until August 1993 while an attack of bone pain involving lower extremites was admitted into hospital. At admission on MRI examination showed a 3x3cm metastatic mass in her left lung. PR was

achieved by the approach of PHA, with adjuvant combination chemotherapy. The remains of only two lymph nodes (each a pea size) in the hilus of her left lung were clearly visible during the course of PHA. Total dosage of PHA 880mg. The patient developed amenorrhea following one month of 15mg Diethylstilbestrol (DES) daily therapy.

Case 4: A 40-year-old man was admitted into hospital on April 27,1996 due to an attack of dyspnea, complicated by progressive weakness, weight loss and loss of appeptide. On CT examination showed much malignant hydrothorax with a 4.5x4.9cm mass in the cavity of his left lung. A regimen was mainly concluded by 6 months of traditional medicine, with the combination of a small dosage of cyclophosphamide (CTX), 5-fluorouracil (5-Fu) and PHA (100mg) at initial period of treatment. A CR with 10 years was achieved and in recovery of his job again.

Case 5: A 10-year-old boy developed the symptoms of dyspnea two months duration at admission on July 5,1996. On CT examination showed much malignant hydrothorax with irregular pleural elliptical masses in his right pleural cavity. The protocol of combination chemotherapy (VCR,1mg/wk; CTX 200- 400mg/ wk; 5-Fu 250mg/day; PHA 10-30mg/day) was given four courses of therapy. A short Complete Remission (CR) after four sequential combination chemotherapy with adjuvant traditional medicine, and showed in the chest X-ray the disappearance of haemorrhagic pleural effusion, with the remains of pleurisy. Total dosage of cytotoxic drugs: VCR 4mg, CTX 600mg, MMC (mitomycin C) 4mg, PHA 870mg. He was allergic rash in respond to PHA administration and in recovery from skin rash when stopping PHA, which possibly indicated over PHA dosage.

Case 6: A 58-year-old lung cancer was admitted into hospital on September 4,2004. He presented his previous history of cough and short breathing following alcohol one month ago. On CT scan showed a 4.5x4x3cm soft mass at hilus pulmonis, complicated by obstructive pneumonia. Histologically under broncho fiberscope, there existed the ingredients of necrotic tissue and some poorly differentiated cancer cells. He was undergoing the combination chemotherapy of PDD plus etoposide in another tumor hospital. The remainder of two courses of combination chemotherapy was continuous to be performed on September 11,2004 and on October 16,2004. A therapeutically protocol consisted of CTX (0.2-0.6g) plus MMC (4 mg) drugs, and interleukin-2 immunotherapy. After having completed chemotherapy, he was treated in other hospital. In this group, there were other 4 cases with a common character of those patients with a mega-enlargement mass. CR and/or PR was achieved by 4-6 courses of intensive combination chemotherapy with adjuvant PHA. All patients were safe to finish intensive timed sequential chemotherapy under supportive therapy of PHA.

Discussion

In the present study, there had been observed the objective response of PHA with chemotherapy in various cancers. It was experienced that PHA was indeed the stimulation of lymphocytic kill cell activity, inducing the generation of interleukin-2 and interferons, preventing those patients undergoing intensive timed sequential chemotherapy from hypoplastic haematopoiesis, thereby exhibiting its anti- neoplastic activity. During the period of PHA treatment, the patients were tolerance well. Recent research on natural IL-2(PHA stimulation)/LAK cells reported in further the adoptive immunotherapy of advanced liver cancer. The complete response of objective regression of cancer with the disappearance of ascites can be achieved in 2/10(20%) of liver cancers [33]. Using Ifosfamide with PHA-LAK cells regimen,3 of 25 obtained CR, and a 44% (11/25) of CR plus PR rate in 25 advanced ovarian epithelial cancer [34]. Under microscope, experimental study on changes were found remarkable lymphocytes and plasmocytes infiltration within tumor tissues. Moreover, A CR (disease- free survival) in 12-year-old children with osteosarcoma was previously reported after prolonged therapy of 5700mg PHA for 32 months (unpublished data). The results (in my group and others) [33-39] seem likely to suggest that a possible strategies of LAK cells/natural IL-2(PHA stimulation) in advanced cancer remains testable.

In the past few years, it has been focused on the association between antineoplastic cytotoxic agents and leukemogenesis, which has moved into the center of caution. Drugs most frequently implicated are alkylating agents, e.g. mulphalan, chlorambucil, busulfan, cyclophosphamide, thiotepa and other cytotoxic drugs such as the nitrosoureas [40-47]. A summary of 91 non-neoplastic patients developed leukaemia after cytotoxic chemotherapy: 39patients were rheumatoid arthritis,13nephropathy, 8renal transplant, 6 multiplesclerosis,5psoriasis,3wegener's granulomatosis,3 Amyloidosis,2 scleroderma,2 scleromyxedema,2 systemic lupus erythematosus, and 8 patients with miscellaneous [41,44,47-54]. 82 of 91 patients received single or multiple alkylating agents. 8 patients were treated with antimetabolites and antipurines (including 6-mercaptopurine, MTX,5-Fu, mitomycin C, daunorubicin, adriamycin). The data have convinced most chemotherapeutics that these agents, especially alkylating agents, had leukemogenicity potential.

Moreover, lots of researches also focused on the establishment of hormones/growth factors and cancers [28,29,55-68]. The data provide evidence that estrogen-dependent cell line (MCF-7) cells under E2 stimulation release some known growth factors activities (CME2, EGF-like, IGF-1-like) capable of replacing E2-induced tumors in vivo in athymic mice. In earliest 1989-90 [27,28,69], the oncogenic fusion of pml/retinoic acid receptor alpha (pml/RARa) was found in t(15;17) acute promyelocytic leukaemia in our team; and in my clinical condition that androgen induced tumors of breast gland in a male with severe aplastic anaemia during the course of methyltestosterone therapy, in which mechanism was possibly mediated by cognating its aberrant oncogenic receptor AR (or also proto-oncogenic receptor) signaling. In animal model, A subcutaneous nodule was clearly shown in the application of continuous rhEGF injection, while no sign of nodule formation was observed following intramuscular rhEGF injection in a rat within 20 days. The subcutaneous nodule was progressive regression after

stopping rhEGF injection for one week (Figure 2, Zhu, *et al.* [70]). In clinical trials of HCC (Hepato-cellular Carcinoma) with sorafenib therapy [71-74], the plasma concentration of HGF in 24 of 30 HCCs was markedly reduced after 12 or 24 weeks of therapy, which is roughly consistent with the decrease also observed in AFP. This Aberrant HGF-HGF receptor (HGFR) activation promotes tumor cell proliferation and metastasis via growth factor receptors and other altered oncogenic receptor pathways such as oncogenic EGFR, GHR (Growth Hormone Receptor) or proto-oncogenic receptor IGF-1R signaling. These data and others implicate that androgen via its (aberrant AR/ER signaling or FGFR-1) receptor signaling or/ and translocated retinoic acid receptor alpha, a steroid and thyroid receptor superfamily, had oncogenic potential [5,6,12,18,20,27-29,66,69,75-79]. In this area, *Dr. Zhu* in 1989s is the first to the discovery of oncogenic receptor concept and its earliest described Ras/Raf/MAPK pathway in cell signaling. This is also the first case involving oncogenic receptor translocated pml/RARa, a steroid receptor fusion in acute leukaemia.

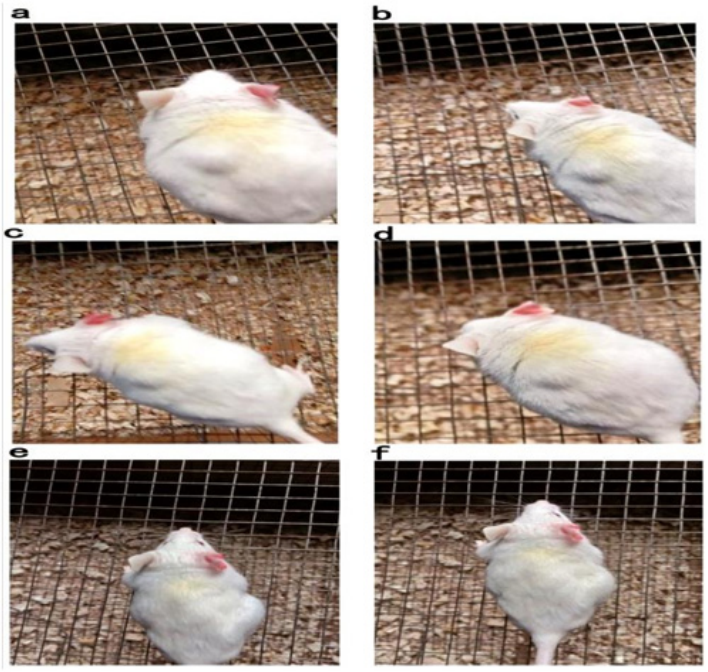

Figure 2: Observations in different rats following rhEGF. A subcutaneous nodule was clearly shown in the application of continuous rhEGF injection, whereas no sign of nodule formation was observed after intramuscular rhEGF injection in a rat within 20 days (Figure 4a- d). Each rat was injected with a total amount of 1 mg of rhEGF solution. The subcutaneous nodule was progressive regression after stopping rhEGF injection for one week (Figure 4e- f) [70].

It is not known at this time whether a single mechanism is involved in both tumor induction and antitumor activity of cytotoxic drugs. In considering the biochemical determinants of antimetabolite action, another prerequisite for doing action is after the binding of membrane Folate Receptor Alpha (FRa) at cell surface in tumors, subsequently intracellular binding to target site (such as dihydrofolate reductase binding by MTX [80-83]). In the presence of excess MTX, all of the enzyme is the form of enzyme -MTX complex. Folate receptor has been characterized [84,85]. Human folate receptor contains 257 amino acid residues [83,86-88]. Moreover, in 42 NSCLC tumor tissues, EGFR mutations correlated with high expression of membrane FR alpha levels [89]. Several mechanisms have also been proposed in which included anthracyclines binding to cellular membranes, followed by DNA intercalation of anthracycline metabolic reduction result in DNA strand breaks, albeit the precise determinants of response of tumor cells to the anthracycline was under investigation. Anthracycline-binding protein has been isolated. Therefore, some of these cytotoxic drugs are presumably mediated by their own cellular specific binding protein, compounds thereby binds DNA, causing DNA synthesis inhibition and induction of chromosomal aberrations as well as immune suppression [90-93].

Add in proof: This work was completed during earlier 1993 to 1997. Abstract once presented in proceeding of 2005 Welt Medizin-Forum und Fachkonferenze uber Krankenhaus-Manangement sowie moderne Medizintechnik, Bremen- Dusseldorf, Germany; and in 2010 ASH Annual meeting abstracts, USA.

Conflict of Interest

None.

Acknowledgement

None.

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