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A Retrospective Study of the Combination of Chemotherapy with Phytohemagglutinin (PHA) in the Treatment of Advanced Cancers

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Abstract

Background: 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 plus PHA during 1993-97. The mean age at onset was 45.3 years (range 10-72 years). All other benign neoplasias were not statistically included in this group. Results: 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 cantharidine and/or traditional medicine, with each 30-years survivors now. A lung cancer was given the combination chemotherapy plus targeting oncogenic receptor EGFR gefitinib therapy, which was in stable disease for 8+ months. Conclusion: In this study, I reported a series of the long follow up of those cured patients with cancers. I experienced that PHA was indeed the stimulation of lymphocytic kill cell activity, thereby exhibiting its anti-neoplastic activity. In previous study, Induction of thyroid neoplasm (thumb size) in 1 postoperative patient with breast cancer was conducted by herb seaweed. The putative mechanism of oncogenic transformation was that iodine contained seaweed drug was participated in 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, tumor development. Moreover, targeting oncogenic receptor therapy in tumours is currently the third setting, and clinically the standard therapy in hospitals worldwide. This will open a new era of cancer target therapy.

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

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1. Introduction

Over past decades, chemotherapy is a common use of cancer treatment. Recent important advances have been increased acceptance in oncology that those patients with disseminated tumors were setted to the chemotherapy with targeting oncogenic receptor (Al-Nedawi *et al.*, 2008; Ascierto *et al.*, 2016; Berjaouia *et al.*, 2025; Deng *et al.*, 2016; Gabitova *et al.*, 2014; Garcia-Fabiani *et al.*, 2021; Hauksdotti and Privalsky, 2001; Judelson and Privalsky, 1996; Kim, 2015; Lee *et al.*, 2006; Lee, 2005; Lee, 2017; Laisney, 2013; Miltra, 2012; Nair *et al.*, 2018; Neil *et al.*, 1988; O'Connor, 2008; Rietveld, 2001; Robinson, 2008; Segalla, 2003; Stutz *et al.*, 2008; Utermark *et al.*, 2012; Wang *et al.*, 2014; Wilmes *et al.*, 2020; Yan *et al.*, 2014; Yang *et al.*, 2014; Zöller, 2018; Zhu, 1992, 2007-19; Zhu and Kumar, 2020), and / or adoptive immunotherapy (Han *et al.*, 1991; Huang *et al.*, 2005; Rosenberg, 1985; Rosenberg *et al.*, 1989; Zhu, 1992, 2010 and 2016-18).

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 anemia. PHA is otherwise the micro-angiogenesis of bone fracture and regeneration of bone. In current study, I summarized the retrospective analyses of the combination chemotherapy with PHA in the treatment of advanced cancers.

2. 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.

3. Results

All 17 patients were in progression at onset diseases. The response of remission were 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%). 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 (8x5 cm) 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 neurotoxity 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.

4. 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 4x6 cm size which was in further confirmed by colonoscope (Figure 1). PR was achieved after one course of 5-Fu (5.5 gram) plus

PHA regimen, with relief symptoms of soft fluid diet even rice gruel. The stools were of normal caliber and consistency. Total dosage of PHA 1410 mg.

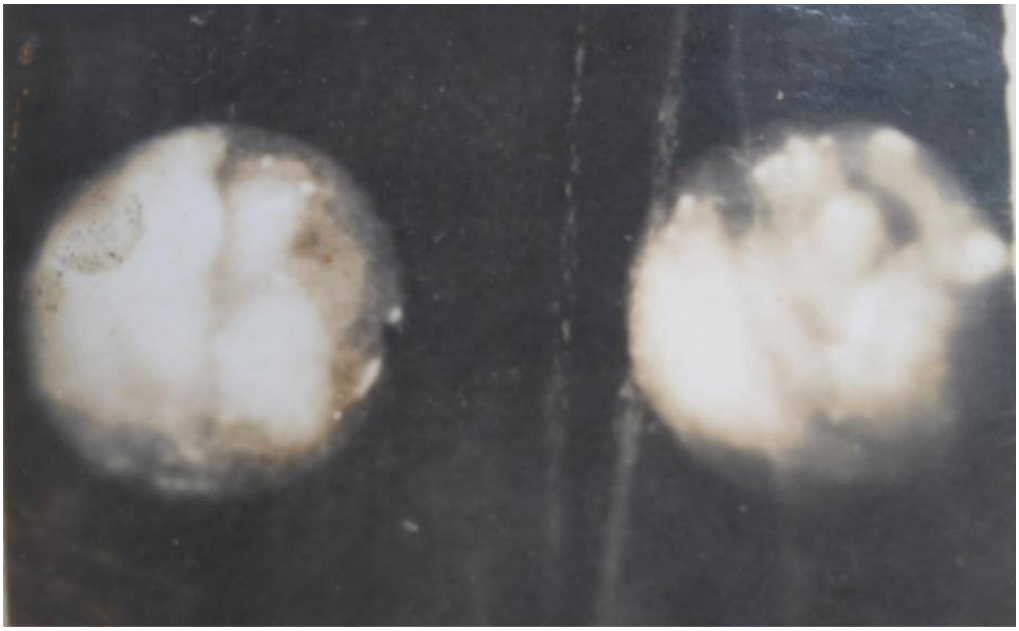

Figure 1 (Case 1): An Ascending Colon Cancer Under Colonscope at Diagnosis

Case 2: A 55-year-old woman was diagnosed as having metastatic palatum cancer on November 5, 1993 when she presented with tumors both in her cavity of the mouth and neck lymphadenopathy. On examination revealed 2 lymph nodes (4x3 cm) 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 nodes palpable. Cures was achieved by use of combination chemotherapy (Vincristine VCR, CTX, 5-Fu, PHA 660 mg), 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 3x3 cm metastatic mass in her left lung. PR was achieved by the approach of PHA, with adjuvant combination chemotherapy. The remains of only two lymph node (each a pea size) in the hilus of her left lung were clearly visible during the course of PHA. Total dosage of PHA 880 mg. The patient developed amenorrhea following one month of 15 mg 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 4.5x4.9 cm mass in the cavity of his left lung. A regimen was mainly concluded by a 6 months of traditional medicine, with the combination of a small dosage of cyclophosphamide (CTX), 5-fluorouracil (5-Fu) and PHA (100 mg) 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 hydrothroax with irregular pleural elliptical masses in his right pleural cavity. The protocol of combination chemotherapy (VCR, 1 mg / wk; CTX 200-400 mg / wk; 5-Fu 250 mg / day; PHA 10-30 mg / 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 hemorrhagic pleural effusion, with the remains of pleurisy. Total dosage of cytotoxic drugs: VCR 4 mg, CTX 600 mg, MMC (mitomycin C) 4 mg, PHA 870 mg. He was allergic rash in respond to PHA administration and in recovery from skin rash when stopping PHA, which possibly indicated over PHA dosage.

In this group, there were other 4 cases with a common characters 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.

5. Discussion

In the present study, there had been observed the objective response of PHA with chemotherapy in various cancers. I 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 hematopoiesis, thereby exhibiting its anti-neoplastic activity. During the period of PHA treatment, the patients were tolerance well. A 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 (Han *et al.*, 1991). 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 (Huang *et al.*, 2005). Under microscope, experimental study on changes were found remarkable lymphocytes and plasmocytes infiltration within tumor tissues. Moreover, A CR (disease-free survival) in a 12-year old children with osteosarcoma was previously reported after prolonged therapy of 5700 mg PHA for 32 months (unpublished data). The results (in my group and others) 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 (Chu, 1982; Coltman, 1982; Gasciato and Scott, 1979; Rosner and Gruwald, 1983; Sieber, 1977; Walker and Bole, 1971; Walpole, 1958). A summary of 91 non neoplastic patients developed leukemia after cytotoxic chemotherapy: 39 patients were rheumatoid arthritis, 13 nephropathy, 8 renal transplant, 6 multiple sclerosis, 5 psoriasis, 3 wegener's granulomatosis, 3 Amyloidosis, 2 scleroderma, 2 scleromyxedema, 2 systemic lupus erythematosus, and 8 patients with miscellaneous (Collman and Dixon, 1982; Fouar *et al.*, 1979; Grunwald and Rosner, 1979; Hocherg and Shulman, 1978; Kahn *et al.*, 1979; Kapadia and Kaplan, 1978; Lebrenchu, 1980; Rosner and Gruwald, 1983; Sultan, 1976). 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 leukemogenic potential.

Moreover, lots of researches also focused on the establishment of hormones / growth factors and cancers (Aaronson, 1991; Berger *et al.*, 2004; Gardner *et al.*, 1938; Goustin *et al.*, 1986; Izumi *et al.*, 2013; Kemp *et al.*, 1989; King, 1991; Newbold *et al.*, 1990; Santon *et al.*, 1986; Singh and Kumar, 2005; Stoscheck and King, 1986; Thomas, 1991; Vickman *et al.*, 2020; Zhu *et al.*, 1992, 2013 and 2020; Zhu and Al-kaf, 2018). 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 earlier 1989-90, Zhu *et al.* (1992 and 2013) found a detection of pml / retinoic acid receptor alpha (pml / RARa) in t(15;17) acute promyelocytic leukemia, and in clinical condition that androgen induced tumors of breast gland in a male with severe aplastic anemia 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 (Zhu *et al.*, 2020). In clinical trials of HCC (hepatocellular carcinoma) with sorafenib therapy (Deng *et al.*, 2016; Yang *et al.*, 2014; Zöller, 2018; Zhu *et al.*, 2019), 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 Met activation promotes tumor cell proliferation and metastasis via growth factor receptors and other oncogenic receptor pathways. 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 (Judelson and Privalsky, 1996; Hauksdotti and Privalsky, 2001; Lee, 2005; Rietveld, 2001; Segalla *et al.*, 2003; Singh and Kumar, 2005; Zhu, 1992 and 2007-19; Zhu and Kumar, 2020; Zhu and Hernando, 2021).

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 (FR) at cell surface in tumors, subsequently intracellular binding to target site (such as dihydrofolate reductase binding by MTX (Mauritz *et al.*, 2008; Rijnboutt *et al.*, 1996; Westerhof *et al.*, 1991; Williams *et al.*, 2020). In the presence of excess MTX, all of the enzyme is the form of enzyme-MTX complex. Folate receptor has been characterized (Colman, 1971; Holm *et al.*, 2015). Human folate receptor contain 257 amino acids (Brigle *et al.*, 1991; Elwood, 1989; Sadasivan and Rothenberg, 1989; Williams *et al.*, 2020). Moreover, in 42 NSCLC tumor tissues, EGFR mutations correlated with high expression of membrane FR alpha levels (Nunez *et al.*, 2012). 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 (Creaven and Rustum, 1983; Pigram *et al.*, 1972; Zunino *et al.*, 1971).

6. Conclusion

This current study aimed to evaluate the efficacy and safety of combination chemotherapy with phytohemagglutinin (PHA) in treating patients with advanced cancers. The study analyzed clinical data (e.g., treatment response, survival time, adverse events) of patients who received either the combination therapy (chemotherapy + PHA) or chemotherapy alone, with a focus on comparing key outcomes between the two groups. The previous results and our trials indicated that this combination therapy showed a higher Objective Response Rate (ORR) and longer Progression-Free Survival (PFS) than the chemotherapy alone group, though statistical significance needs in further verification based on sample numbers and confounding factor adjustment. Regarding safety, the combination chemotherapy did not report a significant increase in severe adverse events (e.g., myelosuppression, gastrointestinal reactions) compared to the chemotherapy alone group, indicating PHA may have a favorable safety profile when added to chemotherapy. Future prospective, large-scale randomized controlled trials are required to further validate the efficacy and safety of chemotherapy combined with PHA for advanced cancers, and to explore optimal PHA dosages and applicable cancer types.

As we known, it is no need to targeting receptor in normal condition and / or non-malignant cells, the current study noted targeting tumors sharing oncogenic receptors. The oncogenic receptor derivative pml / RARa represent a classical instance in really crucial role (over 92-98% positive ratio) of human Acute Promyelocytic Leukemia (APL) leukemogenesis. In this area, Dr George Zhu in 1989s is the first the discovery of oncogenic receptor concept based on original human androgen test and molecular oncogenic pml / RARa fusion in APL, and its earliest described Ras / Raf / MAPK pathway in cell signalling. Now, targeting therapy is shift mainly toward oncogenic receptors or oncogenic receptor kinase within tumours, which is currently the third setting, and clinically the standard therapy in hospitals worldwide. This is beneficial to those tumoral patients. The findings open a new era of cancer target therapy.

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