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Research Article

Glyco-polypeptides (Comosain) and chimeric white blood cell therapy in treating late stage of gynecological and breast cancers

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Abstract

Glyco-polypeptides (Comosain) induced Leucocyte binding ability to tumor surface antigens were studied such as, interleukin 2, 6, 8 and TNF result in fibrinolysis, anti-metastatic effects. Using different concentration of Comosain proteinases in various types of cancer cell. Anti- cancer effects were achieved in carcinoma of breast, uterus, cervix and ovary. Investigation of anti-metastatic effects in Comosain were carried out in a double blind study; low dose cohort was on 10 mg/kg/day, and high dose cohort was on 50 mg/kg/day for a period of more than six to eight months. A total number of 61 patients with 3rd and 4th stage of refractory solid tumors were enrolled, who at least previously failed on two regimens of chemotherapy and /or on radiation therapy. In this study, we mainly emphasized the test result of Glyco-polypeptides in treatment of solid tumors. The low dose group patients were completely ineffective and were transferred to high dose to continue treatment. The rates of complete response (CR) and partial responses (PR) in high dose cohort are astonishing with rate of 68 % (42/61) and 19 % (12/61) respectively. Stable diseases (SD) and Progressive diseases (PD) in high dose cohort both are with rate of 6.5% (4/61). The implications and results of the findings are discussed.

Since 1978, Dr. Maurer, Dr. Eckert, Dr. Harrach (5, 9,11,12, 23, 24, 25, 42, 45, 31) and many other authors studied and found that Glyco-polypeptides (Comosain) have superb anti- cancer effects. Our findings in treating various type of cancers are very astonishing and effective, when Comosian are using in large dose and prolong period of times prefer more than 6 months.

PURPOSE

Administered of oral Glyco-polypeptides (Comosain) in cancer treatment in nonclinical trials has been reported as early in 1968 by Wolf M, & Ransberger k (1). In vitro and animal studies have suggested of anti-metastatic effect for Glyco-polypeptides (Comosain). Batkin & Taussig (2,3) in 1988 reported that orally administered Glyco-polypeptides (Comosain) reduced the incidence of pulmonary metastasis in Lewis lung cancer cells in mice. In recent years, 1988 Batkin & Taussig (4) suggested the antitumor mechanisms are due to fibrinolytic effect in Glyco- polypeptides (Comosain). Taussig & Batkin in 1988 (5) discovered that Glyco-polypeptides (Comosain) has anti-Platelet aggregation effects. Taussig and Batkin in 1985 (5) also discovered Inhibition the growth of tumor cells such as Lewis lung carcinoma, V-8 lymphoma, MC1-1 acites, KATO-gastric carcinoma cells. Maurer & Hozumi, in 1994 (6) Discovered Glyco-polypeptides (Comosain) Induced Differentiation in leukemic cells. Hale, & Haynes in 1992 (7) and Cantrell et. in 1996 had suggested that due to Major Histocompatibility Protein Kinases,

such as MMAPK (Major Mitogen Activating Protein Kinase) and TPK (Tyrosine Phosphorylation Kinase) inhibitors were activated by Glyco-polypeptides (Comosain). T-cell activation and cascade production of Interleukin 2, 6, 8, and TNF-a (Tumor Necrotizing Factors) via CD-2, CD-3 surface antigen of WBC.

Garbin, Harrach, Eckert, & Maurer in 1994 (15) and Hale, & Haynes in1992 (7) also suggested that Glyco-polypeptides (Comosain) will reduce surface antigens of CD-44, CD-44v, CD-44s, CD45, & CD 47 in tumor cells of breast carcinoma.

From the experimental studies above, we conclude that activation of Glyco-polypeptides (Comosain) in lymphocytes and T-cells have anti-metastatic effects both in vitro and in vivo.

In the present study, we compared the modulation of low dose cohort and high dose cohort of Comosain administration to the

patients with stage 3, and stage 4, refractory solid tumors, which including various types of carcinoma of breast, uterus, cervix and ovarian. All patients failed previously on at least two regimens of chemotherapy and /or failed on radiation therapy, The treatment were carried out for at least 24 to 28 weeks, the complete blood count, liver, renal function, hematopoietic elements, tumor markers were evaluated at an interval of every 2 to 4 weeks, the computerized tomography scan were performed at an interval of every 3 to 4 months. The size of tumors were measured, the tumor markers were recorded for the evaluation of complete response (CR), partial response, (PR), stable disease (SD), and progressive disease (PD) according to the Standard Response Criteria of National Cancer Institute (NCI). The Common toxicity were recorded by using NCI's Standard Toxicity Criteria. The results of CR and PR were promising and astonishing when Comosain were administered in patients of high dose group.

MATERIALS AND METHODS

Glyco-polypeptides (Comosain) were purchased from Natural Organics Laboratories, Amityville, N.Y., Capsules to contain Glyco-polypeptides (Comosain) were purchased from Capusugel Co. Greenwood, North Carolina. Comosain were analysed by using SDS-Polyacryl- Amide Gel Electrophoresis (SDS-PAGE), Cation Exchange Chromatography (CEC), Florescence High Performance Liquid Chromatography (FPLC) to determinate the purity and separation of Glyco-polypeptides (Comosain) fraction of F1, F2, F3, F4, F5, F6, F9 in stem Glyco-polypeptides (Comosain) (Harrach et al 1994 (9) were detected by Amperometric detection. Monosaccharides fraction are L-fructose, D-galactosamine, D-glucosamine, D-xylose, D-mannose, D-glucose, D-galactose, D-fructose, and Deoxyribose.

Clinical Application and Study protocol.

Patients Eligibility and Selection (Total number of patients: 61)

- Patients with stage III and IV solid cancer of breast, uterus, cervix and ovarian with tissue proof of well-documented malignancies, whether by tissue biopsies and have not been helped by conventional radiation therapy and/or chemotherapies for at least two separated regimens are eligible for this study.
- Or patients must have no available therapy known to provide clinical benefit. For example, the breast cancer patients must have failed at least 2 chemotherapy regiments in the metastatic setting.
- Additionally

Patient's age is between 18 and 95+ years, not taking anticoagulants, have no history of abdominal fistula, gastro-enteral perforation, peptic ulcer diseases, or intra-abdominal abscess within 4 months prior to study enrollment, and patient has not had major surgery within 4 weeks prior to study enrollment, and other requirements are same as NCI's criteria. Also, Patient does not have uncontrolled hypertension, diabetes, or cardiac arrhythmia, and not allergic to Glyco-polypeptides (Comosain) -containing products, not pregnant or breastfeeding. Patient's WBC count < 3k/uL, hemoglobin < 9.0 g/dL, platelet counts must be < 100,000/uL, and INR < 1.5 have no significant abnormal hepatic and/or renal function.

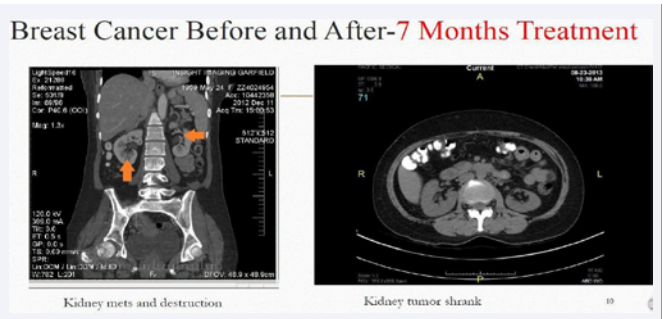


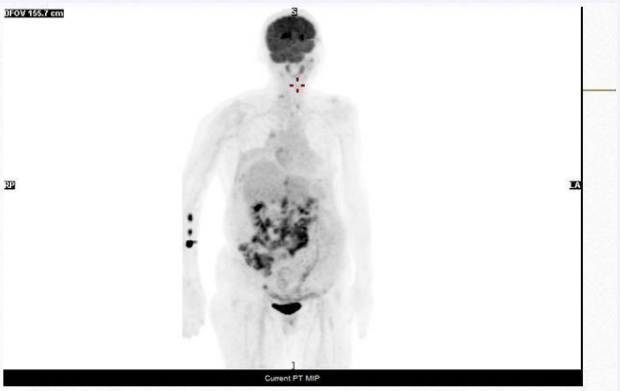
Figure 1 Breast cancer pre and post treatment (Kidney mets).

Figure 2 Breast cancer pre and post treatment (Bone Mets).

Figure 3 Breast cancer pre and post treatment (Liver Mets, 9.2cm shrinkage to 2.6cm).

Patient's tumors are measurable between 0.2 – 10+ cm in size and number between 1–15+. All measurable tumors that have spread to the bones, liver, lung, kidney, and abdomen will be included in the data analysis.

Patients who are eligible for this study will be randomly assigned to either the low dose cohort or the high dose cohort by



Stage 4, ovarian CA with massive intra abdomen intraabdominal spread, with 3.5 months treatment, the CA-125 down to normal 14 IU. Patient still alive after 10 years. Now she is 92 years old alive and well.

Figure 4 Ovarian cancer pre and post treatment.

a coin toss. Each study subject will be assigned a patient number for the purpose of this study.

Methods of Study

The dose of Comosain at 50 mg /kg/day is extrapolated from *in vivo* animal studies, and determined to be safe by a safety study on healthy human subjects.

The high dose cohort will be given Comosain at 50 mg /kg/day (at a body weight of 50- 60 kg) to a maximum of 2400 mg / day and divided into 2 doses/day of 1200 mg/dose, and taken with meals. Low dose Cohort patients will be given Comosain at 500 mg /day, divided into two doses of 250 mg/dose and taken with meals.

High Dose Cohort – The number of patients will be at least 35.

Low dose Cohort--The number of patients will be at least 26.

- Blood/laboratory tests will be scheduling every 2-4 weeks, which include CBC, Chemistry- 7, Chemistry-24, liver and renal function, CEA, CA125, CA153, CA199, PSA,TSH, alfa-Feto- Protein and other tumor markers.
- Radiological tests will be assessed every 3-4 months.
- Each patient will be also assessed every 4 weeks for any side effects that they may have experienced. Using NCI standard toxicity criteria for hematology, renal, and hepatic system evaluation.
- Adverse events, serious adverse events reporting information also using NCI criteria

Duration and Route of Administration

The patients will be evaluated by blood tests and/or CT scans at the end of each 6 weeks cycle and at six months for signs of disease progression. If the disease did not progress, then treatment will continue, and the patient will be evaluated every six months thereafter until the investigator determines otherwise. If the disease did progress, then the patient will be taken off the study. On the Humanitarian base, the low dose group patients will be transferred to the high dose group due to lack of efficacy in the treatment.

Results 1

At the end of six months, each patient will be determined whether or not to continue with this therapy and assess the efficacy of the therapy by using NCI Standard response Criteria:

- Evaluation of Target Lesions

(A) Complete Response (CR): Disappearance of all Target lesions, and lymph nodes must be reduced < 10mm.

(B) Partial Response (PR): At least a 30 % decrease in the sum of the diameters of target lesions compared with the baseline sum diameters.

(C) Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions compared with the smallest sum on study. In addition, the sum must demonstrate an absolute increase of at least 5 mm. The appearance of new lesions is also considered progressions.

(D) Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference to the smallest sum diameters while on study.

- Evaluation of Non-Target Lesions

(A) Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be < 10mm short axis.

(B) Non-CR/ Non-PD: Persistence of one or more non-target lesion(s) and /or maintenance of tumor marker level above the normal limits.

(C). Progressive Disease (PD): Appearance of one or more new lesions and/ or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status.

Results 2

Age distribution, all the patients are mainly 60 years of age or above. The disease classification and distribution are as following: breast carcinoma account for 17/61, in uterus carcinoma the incidence is 8/61, in cervix carcinoma the incidence is 7/61; in ovarian carcinoma the incidence is 10/61 (Table 1).

The tumor markers such as CEA,CA-125 and CA-153 are been monitored, their values are corresponding to the tumor masses, they return to normal value when tumor have CR, and when the tumor progress the tumor marker value are elevated.

The serious adverse effect in toxicity in both groups are not observed, there were no serious hematopoietic or hepato-renal toxicity, no anaphylactic reaction or life threaten events.

There were rarely minor side effects such as nausea, vomiting, diarrhea, palpitation, headache, insomnia, pruritus, urticaria, and skin rash. We conclude that Glyco-polypeptides (Comosain, Ananases) administered in an amount of 2500 to 3000 mg/day to the patients with average body weight 60kg are effective and non-toxic.

Table 1: The overall clinical response rate in high dose group patient:

	CR	PR	PD	SD
Breast CA	53% (17/32)	28% (9/32)	9% (3/32)	9% (3/32)
Ovarian CA	91% (10/11)	9% (1/11)	0% (0/11)	9% (1/11)
Uterus CA	72.7% (8/11)	18% (2/11)	9% (1/11)	0% (0/11)
Cervix CA	100% (7/7)	0%	0%	0%

CONCLUSION

In summary, Glyco-polypeptides (Comosain, Ananases) administration in double-blind study showed effectiveness only in patients with high dose cohort of 50 mg/kg/day regimen. The low dose cohort showed no efficacy at all. Both groups did not show serious adverse effects such as leukopenia, anemia, hepato-renal toxicity, anaphylactic reaction, and life-threaten events.

Minor adverse effects such as nausea, vomiting, diarrhea, urticaria, insomnia, palpitation, pruritus, and headache occurred rarely.

The remarkable cancercidal effects probably due to massive production of Interleukin-II, VI, VIII, and tumor necrotizing factors from CD-2, CD-3 in monocytes and lymphocytes (WBC). The fibrinolytic effects on tumor surface antigens of CD-44, CD-44V, CD-44S, CD-45, and CD-47 which induce dehydration, necrosis, and possible calcification in the tumor cells. This action mechanism of Glyco-polypeptides (Comosain, Ananases) is mainly attributed to inhibition of 2 kinases: Major Mitogen Activating Protein Kinases and Tyrosine Phosphorylation Kinases. In the WBC culture test with concentration of Glyco-polypeptides (Comosain, Ananases) in an amount of 1 mg/ml will increase the production of Interleukin II by 400 times/10^6 WBC, Interleukin-6 by 650 time/10^6 WBC, and the TNF by 42 times/10^6 WBC.

The results in the high dose group patients showed remarkable CR rates of 53% in breast cancer; 91% in ovarian cancer, 72.7% in uterus cancer; and 100% in cervix cancer. Dr. HR Maurer in his complimentary tumor therapy also showed Glyco-polypeptides (Comosain, Ananases) in an amount of 1000-to-3000 mg/day for the period of 1 to 3 years had good anti- tumor effect, no severe side effects nor any life threaten events.

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