

Chemotherapy-induced immunosuppression is restored by a fermented soybean extract: a proof of concept clinical trial[☆]

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Abstract

Depressed activity of natural killer (NK) cells is often associated with a higher incidence of infection and tumor recurrence. Despite evidence that NK cell activity is depressed after chemotherapy, there have been no clinical trials reporting the amelioration of this side effect. ChemoYoung, a fermented soybean extract, has been shown to activate NK cells *in vivo*. We conducted a randomized clinical trial to examine the effect of ChemoYoung on the restoration of NK cell activity during chemotherapy. Thirty-two patients were recruited for a self-controlled, randomized, crossover chemotherapy program with 2 consecutive, identical dose intensity chemotherapy cycles, with or without the oral intake of ChemoYoung during each cycle of chemotherapy. Patients were administered ChemoYoung (MicroBio Biotech Comp, Taipei, Taiwan) for 21 days during chemotherapy. The NK cell activity, T4/T8 ratio, NK cell number, and serum interleukin (IL) 2 level on day 21 of each cycle were compared. The mean white blood cell nadir, T4/T8 (%), NK number (%), and IL-2 serum level (ng/mL) of the combined group vs the chemotherapy-alone group were 3096/ μ L vs 2404/ μ L, 35.3/15.2 vs 29.2/13.7, 19% vs 17%, and 3.2 vs 2.0, respectively (all $P > .1$). However, the NK activity was 13.4 ± 10.3 for the combined treatment group and 4.5 ± 3.2 for the chemotherapy-alone group ($P = .001$). Natural killer cell activities were significantly reduced in patients who received chemotherapy without the adjuvant use of ChemoYoung. A trend to a better quality of life was also noted as assessed using the instrument of the European Organization for Research and Treatment of Cancer core questionnaire.

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Keywords:

Human cancer; Natural killer cells; Fermented soybean extract; Chemotherapy side effects; Immunosuppression, quality of life

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1. Introduction

Cytotoxicity mediated by natural killer (NK) cells is an important defense mechanism against cancer. Depressed NK cell activity has been shown to be associated with a higher incidence of tumor recurrence or metastasis in many animal models [1–3]. Natural killer cell activity is significantly reduced in patients with cancers of head and neck, gastric,

lung, and breast as compared with healthy individuals [4–7]. The depressed NK activity is closely associated with a higher tumor stage, poor prognosis, and higher recurrent or metastatic rates [8,9]. Chemotherapy is generally regarded as an immune suppressant if moderate cytotoxic doses are applied. However, the therapeutic effect from chemotherapy may, in turn, increase immunity due to the partial elimination of suppressive factors from tumor cells. Therefore, immune function has been shown to be affected by chemotherapy in both negative [10] and positive [11,12] ways. Researchers hope that the combination of chemotherapeutic and immunotherapeutic approaches can be used in cancer treatment for 2 reasons: (1) restore depressed NK activity and (2) enhance immunity synergistically when chemotherapy has a positive effect on immunity [13].

During chemotherapy, the quality of life is often compromised, and poor appetite and fatigue are the most common and distressing problems in patients with cancer [14]. The prevalence of fatigue has been reported to range from 50% to 90% among patients with cancer, and 80% have their daily life affected; in fact, 28% of patients have been precluded from working entirely [15–17]. Anemia, dehydration, malnutrition, metabolic derangements, anorexia, and infection all have been proposed to be the cause of cancer-related fatigue and poor appetite. Because the etiology and mechanisms underlying fatigue and poor appetite in cancer patients are multifactorial, there is considerable variation in current practice regarding the management of such accompaniments of cancer, including antidepressants, glucocorticoids, psychostimulants, appetite stimulants, and transfusion [18].

ChemoYoung (MicroBio Biotech Comp, Taipei, Taiwan) is a fermented product produced from soymilk with microorganisms such as *Lactobacillus acidophilus*, *L. bulgaricus*, *Bacillus koernchen*, *Micrococcus lactis*, and yeasts. The fermented soup is collected, sterilized, and used as a health food that has been sold in the marketplace for many years. ChemoYoung is a conditioned medium derived from an anaerobic microbial fermented product; it contains natural antibiotics to inhibit other bacterial species from growing but helping normal bacterial flora to grow. ChemoYoung was found to have an immune-modulating effect in both in vitro and in vivo experiments where significant activation of NK cells was observed (unpublished data). There is evidence that ChemoYoung is a potent 15-lipoxygenase enzyme activity inhibitor, and many inflammatory mediators are also inhibited (unpublished data). In vitro studies have demonstrated that the fermented soup has excellent antioxidant activities, such as scavenging of free radicals and inhibition of lipid peroxidation [19].

The primary aim of this study was to evaluate the effect of ChemoYoung on the restoration of NK activity depression during chemotherapy. This is the first dietary supplement trial aimed at boosting NK cell activity during chemotherapy.

2. Methods and materials

2.1. Study design

This was a prospective, randomized, open-label, self-control, and crossover comparative study of oral ChemoYoung plus chemotherapy vs chemotherapy alone in patients with a variety of advanced cancers. The patient eligibility criteria were as follows: (1) a histologic- or cytologic-confirmed malignancy; (2) participation in an active chemotherapy program for at least one more cycle with the same regimen; (3) recovery from previous chemotherapy with resolution of all treatment-related toxicities for at least 2 weeks, with bone marrow recovery as evidenced by a white blood cell (WBC) count above 3500/mm³, a platelet count above 100,000/mm³, and a hemoglobin level of above 10 mg/dL; (4) a performance status of 0 to 2 according to the Eastern Cooperative Oncology Group (ECOG) scale; (5) adequate renal function with a serum creatinine below 2 mg/dL, adequate liver function with a serum bilirubin level less than 2 times the reference range, and a AST (aspartate aminotransferase)/ALT (alanine aminotransferase) less than 3 times the reference range; (6) ability to complete a quality of life scale questionnaire; and (7) age between 18 and 75 years. The exclusion criteria were as follows: (1) an ECOG performance scale of 3 and above, (2) inability to tolerate oral ingestion, (3) incomplete recovery from previous chemotherapy toxicities, and (4) poor compliance. The enrollment began in July 2001 and ended in March 2003. Patients were evaluated for eligibility criteria and signed informed consent before entering the study. A randomization number was provided by the Cancer Registry Computer Service. This study was approved by the institutional review board of the Veterans General Hospital in Taipei.

2.2. Treatment planning

Cancer types and chemotherapy regimens were not restricted in this study. Patients were randomized to receive ChemoYoung either on the first or second chemotherapy cycle. The same dose intensity and schedule of chemotherapy regimen between the 2 consecutive cycles were required. The interval between the 2 chemotherapy cycles was 28 days. ChemoYoung began from the first day of chemotherapy up to 21 days. There was a 1-week rest before the next cycle of chemotherapy to prevent a carryover effect. The dose of ChemoYoung was 5 mL in the morning and 3 mL in the afternoon, before meals. End points of this study were the change in NK cell activity and a change in the quality of life, as measured by the European Organization for Research and Treatment of Cancer core questionnaire (EORTC/QLQ-C30). The EORTC/QLQ-C30 questionnaire has 30 ordinal scale items that include multi-item domains for physical function, emotional function, social function, pain, and global quality of life [20]. There is a 10-cm Visual Analogue Scale (VAS) to assess the degree of fatigue, appetite, and constipation. Patients were asked to assess their quality of life (QOL) using the VAS over the previous week

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