American Institute of Integrative Oncology
RESEARCH & EDUCATION

Foundations of Integrative Oncology
COURSE

GRAND ROUNDS CALL
With Dr. Nalini Chilkov
May 8th, 2019
Second Wednesday of Every Month
5:30 PM Pacific / 6:30 PM Mountain / 7:30 PM Central / 8:30 PM Eastern

CLINICAL PEARL: Nutraceuticals and Botanicals That Influence Cancer Related Cognitive Impairment
Cancer Related Cognitive Impairment: Selected Nutraceuticals and Botanicals
SEE SLIDES

CASE STUDY: 37yo F Recently Dlagnosed Chronic Lymphocytic Leukemia (CLL)
Submitted by Dr. Shiroko Sokitch, MD
Overview: see PDF Case Study Submitted by Dr. Sokitch_CLL
Core Questions: Biomarkers, Tx Plan for EBV , Tx Plan for CLL
Recommendations: see PDF AIIORE CASE STUDY_CLL_TxPlan

RESEARCH: The Effectiveness of Traditional Chinese Medicine in Treating Patients with Leukemia
Wang, Y., Liao, C., Chen, H., Hsieh, C., & Li, T. (2016). The Effectiveness of Traditional Chinese Medicine in Treating Patients with Leukemia. *Evidence-Based Complementary and Alternative Medicine, 2016*, 1-12. doi:10.1155/2016/8394850

RESEARCH: Integration of Chinese Herbal Medicine Therapy Improves Survival of Patients With Chronic Lymphocytic Leukemia: A Nationwide Population-Based Cohort Study
Fleischer, T., Chang, T., Chiang, J., Hsieh, C., Sun, M., & Yen, H. (2016). Integration of Chinese Herbal Medicine Therapy Improves Survival of Patients With Chronic Lymphocytic Leukemia. *Medicine, 95*(21). doi:10.1097/md.0000000000003788

RESEARCH: A new promising way of maintenance therapy in advanced ovarian cancer: a comparative clinical study.
Kiselev, V. I., Ashrafyan, L. A., Muyzhnek, E. L., Gerfanova, E. V., Antonova, I. B., Aleshikova, O. I., & Sarkar, F. H. (2018). A new promising way of maintenance therapy in advanced ovarian cancer: A comparative clinical study. *BMC Cancer, 18*(1). doi:10.1186/s12885-018-4792-9

The aim of this study was to evaluate the efficacy of five-year maintenance therapy with indole-3-carbinol (I3C) as well as I3C and epigallocatechin-3-gallate (EGCG) conducted before, during, and after combined treatment compared with combined treatment alone in advanced ovarian cancer.

METHODS: 300 patients 60 patients per arm
Patients with stage III-IV serous ovarian cancer were assigned to receive

combined treatment plus I3C 200mg (arm 1),

combined treatment plus I3C 200mg and EGCG 200mg (arm 2),

combined treatment plus I3C and EGCG plus long-term platinum-taxane chemotherapy (arm 3), combined treatment alone without neoadjuvant platinum-taxane chemotherapy (control arm 4), combined treatment alone (control arm 5).

Combined treatment included neoadjuvant platinum-taxane chemotherapy, surgery, and adjuvant platinum-taxane chemotherapy.

The primary endpoint was overall survival (OS). Secondary endpoints were progression-free survival (PFS) and rate of patients with recurrent ovarian cancer with ascites after combined treatment.

Dr. Chilkov Comment:

Recommended daily dosing: I3C 500-1000mg EGCG 1000-4000mg

RESULTS:

After five years of follow-up, maintenance therapy dramatically prolonged PFS and OS compared to control.
Median OS was
60.0 months (95% CI: 58.0-60.0 months) in arm 1, I3C
60.0 months (95% CI: 60.0-60.0 months) in arms 2 and 3 I3C EGCG + long term CT
46.0 months (95% CI: 28.0-60.0 months) in arm 4, no neoadjuvant , no long term CT
44.0 months (95% CI: 33.0-58.0 months) in arm 5. No long term CT

Median PFS was
39.5 months (95% CI: 28.0-49.0 months) in arm 1, I3C
42.5 months (95% CI: 38.0-49.0 months) in arm 2, I3C 200mg EGCG 200mg
48.5 months (95% CI: 39.0-53.0 months) in arm 3, I3C 200mg EGCG 200mg + LT CT
24.5 months (95% CI: 14.0-34.0 months) in arm 4, no neoadjuvant CT no long term CT
22.0 months (95% CI: 15.0-26.0 months) in arm 5. No long term CT no long term CT

The rate of patients with recurrent ovarian cancer with ascites after combined treatment was significantly less in maintenance therapy arms compared to control.

RESEARCH: Melatonin cytotoxicity in human leukemia cells: relation with its pro-oxidant effect.

CELL STUDY

Buyukavci, M., Ozdemir, O., Buck, S., Stout, M., Ravindranath, Y., & Savasan, S. (2006). Melatonin cytotoxicity in human leukemia cells: Relation with its pro-oxidant effect. *Fundamental and Clinical*

Pharmacology, 20(1), 73-79. doi:10.1111/j.1472-8206.2005.00389.x

Abstract

Melatonin has a variety of functions in human physiology and is involved in a number of pathological events including neoplastic processes. The tissue protective actions of melatonin are attributed to its antioxidant activity though, under certain conditions, melatonin might also exert oxidant effects, particularly in cancer cells. This study evaluated the effects of 10(-5) and 10(-3) m concentrations of melatonin on human leukemia cells. Moderate cytotoxic effects of melatonin at 10(-3) m concentrations were observed in CMK, Jurkat and MOLT-4 cells which was associated with significant reactive oxygen species (ROS) generation. Melatonin treatment was not associated with significant cytotoxicity in HL-60 cells, although the generation of ROS was significantly increased. K562 and Daudi cells did not appear to be effected by melatonin treatment. Cellular membrane lipid peroxidation was not influenced by melatonin with the exception of CMK cells. Cell cycle kinetics were not affected in melatonin-treated samples, again with the exception of CMK cells which showed **increased apoptosis.** Melatonin, therefore, induces the production of ROS that may be associated with cytotoxicity depending on the concentration of melatonin in some leukemia cells and **does not appear to stimulate leukemia cell growth.** These pro-oxidant actions of melatonin may assist in limiting leukemic cell growth.

PMID: 16448397

RESEARCH: Melatonin: does it have utility in the treatment of haematological neoplasms?

Li, T., Yang, Z., Jiang, S., Di, W., Ma, Z., Hu, W., . . . Yang, Y. (2017). Melatonin: Does it have utility in the treatment of haematological neoplasms? *British Journal of Pharmacology, 175*(16), 3251-3262. doi:10.1111/bph.13966

Abstract

Melatonin, discovered in 1958 in the bovine pineal tissue, is an indoleamine that modulates circadian rhythms and has a wide variety of other functions. Haematological neoplasms are the leading cause of death in children and adolescents throughout the world. **Research has demonstrated that melatonin is a low-toxicity protective molecule against experimental haematological neoplasms,** but the mechanisms remain poorly defined. Here, we provide an introduction to haematological neoplasms and melatonin, especially as they relate to the **actions of melatonin on haematological carcinogenesis.** Secondly, we summarize what is known about the mechanisms of action of melatonin in the haematological system, including its **pro-apoptotic, pro-oxidative, anti-proliferative and immunomodulatory actions.** Thirdly, we discuss the **advantages of melatonin in combination with other drugs against haematological malignancy**, as well as its other benefits on the haematological system. Finally, we summarize the findings that are contrary to the suppressive effects of melatonin on cancers of haematological origin. We hope that this information will be helpful in the design of studies related to the therapeutic efficacy of melatonin in haematological neoplasms.

LINKED ARTICLES: This article is part of a themed section on Recent Developments in Research of

Melatonin and its Potential Therapeutic Applications.

To view the other articles in this section visit http://onlinelibrary.wiley.com/doi/10.1111/bph.v175.16/issuetoc.

 PMID:28880375 PMCID: PMC6057911 DOI: 10.1111/bph.13966

RESOURCE: KNOW Knowledge of Naturopathic Oncology Website

https://www.knowoncology.org/

KNOW is a dynamic clinical and educational tool that provides summaries of up-to-date- research in integrative oncology.

KNOW is designed to help you quickly access pertinent information to make evidence-informed decisions.

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3. Buyukavci, M., Ozdemir, O., Buck, S., Stout, M., Ravindranath, Y., & Savasan, S. (2006). **Melatonin cytotoxicity in human leukemia cells: Relation with its pro-oxidant effect.** *Fundamental and Clinical Pharmacology,20*(1), 73-79. doi:10.1111/j.1472-8206.2005.00389.x
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5. Fleischer, T., Chang, T., Chiang, J., Hsieh, C., Sun, M., & Yen, H. (2016). **Integration of Chinese Herbal Medicine Therapy Improves Survival of Patients With Chronic Lymphocytic Leukemia.** *Medicine,95*(21). doi:10.1097/md.0000000000003788
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3348-3356. doi:10.1002/cncr.25098

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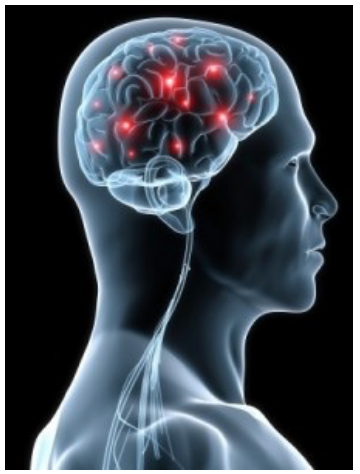
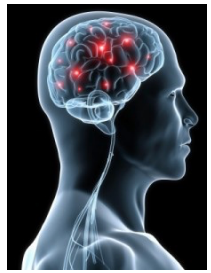
CANCER RELATED COGNITIVE IMPAIRMENT



Selected Nutraceutical and Botanical INTERVENTIONS

Dr Nalini Chilkov, Founder

CHEMOTHERAPY INDUCED COGNITIVE IMPAIRMENT



A neuropsychological syndrome induced by pharmacologic agents used in oncologic therapy.

Cognitive Decline ranging from mild inability performing some tasks to serious memory, attention and executive function impairments

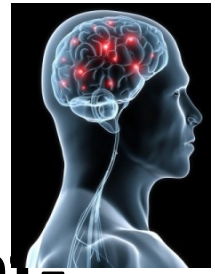
IMPACT: 18% and 78% of breast cancer patients report dyscognition soon after initiating chemotherapy treatment

Symptoms have been reported to **persist** for months to years **in ~35% of patients in disease-free remission**

Cancer-related cognitive dysfunction may be long-term and has been reported to **last 5–10 and up to 20 years** after successful treatments in the cancer survivors

Koppelmans V, Breteler MM, Boogerd W, et al. Neuropsychological performance in survivors of breast cancer more than 20 years after adjuvant chemotherapy. *J Clin Oncol*. 2012;30(10):1080–1086.

Selected References



Ahles TA, Root JC, Ryan EL. **Cancer- and cancer treatment-associated cognitive change: an update on the state of the science**. J Clin Oncol. 2012;30(30):3675–3686

Wefel JS, et al. **Acute and late onset cognitive dysfunction associated with chemotherapy in women with breast cancer**. Cancer. 2010;116(14):3348–3356

VITAMIN D

25 OH VIT D
Goal 55-80 ng/ml

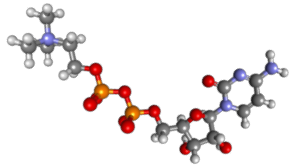
Participants moderately **deficient in Vitamin D** had a 53% increased risk of developing dementia of any kind, and the risk increased to 125% in those who were severely deficient in vitamin D.

N=58 95% CI

Littlejohns TJ, et al. **Vitamin D and the risk of dementia and Alzheimer disease**. *Neurology*. 2014;83(10):920-928.

CITICHOLINE : A Choline Donor (Cytidine-5-diphosphate choline) **250mg-1000mg bid**

- **Inhibits Apoptosis** associated with cerebral ischemia
- **Potentiates Neuroplasticity**
- Choline Source for biosynthesis of membrane phospholipids, Acetylcholine and Phosphatidyl Choline
- **Increases Brain Metabolism**
- **Neuroprotective Effects during hypoxia and ischemia**



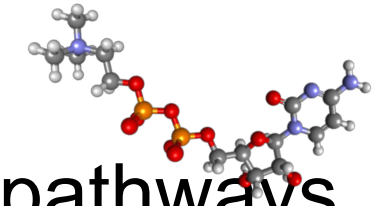
N=24. p< 0.005

Methods Find Exp Clin Pharmacol. 1997 Apr;19(3):201-10.
Citicoline improves memory performance in elderly subjects. Alvarez XA et al

CITICHOLINE Cytidine-5-Diphosphocholine (CDP-choline)

250-1000mg bid

Potentiates neuroplasticity



- Natural precursor of phospholipid synthesis
- Serves as a choline source in the metabolic pathways for biosynthesis of acetylcholine
- Increases Sirtuin 1 (SIRT 1) expression N=60. p=0.03

McGlade E et al.**Improved attentional performance following citicoline administration in healthy adult women**. *Food Nutr Sci*. 2012;3:769–773.

CITICHOLINE (CDP-choline) Cytidine-5-Diphosphocholine 250mg-1000mg bid

- Improves both the immediate and delayed recall of words and objects
- Ameliorates short & long-term memory, attention, perceptual-motor ability
- Ameliorates behavioral and emotional control
- Improves verbal memory functioning in older individuals with relatively inefficient memory

Clin Interv Aging. 2015; 10: 1421–1429. REVIEW **The role of citicoline in cognitive impairment: pharmacological characteristics, possible advantages, and doubts for an old drug with new perspectives**

Pietro Gareri,

ACETYL-L-CARNITINE NEUROREGENERATION

1-3 grams/day

ACL SUPPORTS
Neuronal Survival and Restoration in CNS and PNS
Artemin Neurotrophic Factor
Glial Cell Derived Neurotrophic Factor

Pisano C et al. **Paclitaxel and Cisplatin-induced neurotoxicity: a protective role of acetyl-L-carnitine**. *Clin Cancer Res*. 2003;9(15):5756–5767.

Vivoli E et al. **Acetyl-L-carnitine increases artemin neurotrophic factor level and prevents neurotrophic factor alterations during neuropathy**. *Neuroscience*. 2010;167(4):1168–1174.

Michele Malaguarnera et al
Metabolic Brain Disease December 2011, 26:281

ACETYL L-CARNITINE improves cognitive functions in severe hepatic encephalopathy
A randomized and controlled clinical trial

RDBCT (n=61) with severe hepatic encephalopathy. The 2 groups received either **2 g ALC twice a day** (*n* = 30) or placebo (*n* = 30) for 90 days. 88% of patients treated with ALC vs 72% of patients treated with placebo showed **a significant improvement in EEG, cognitive deficits, reduction of ammonia**

Curcumin and Cognition 3-6g/day

- Crosses Blood Brain Barrier
- Supports Axonal Regeneration
- Increases Brain Derived Neurotrophic Factor
- Reduces NeuroInflammation
  - linked to mood dysregulation and cognitive function
- Stimulates Clearance of beta amyloid plaques

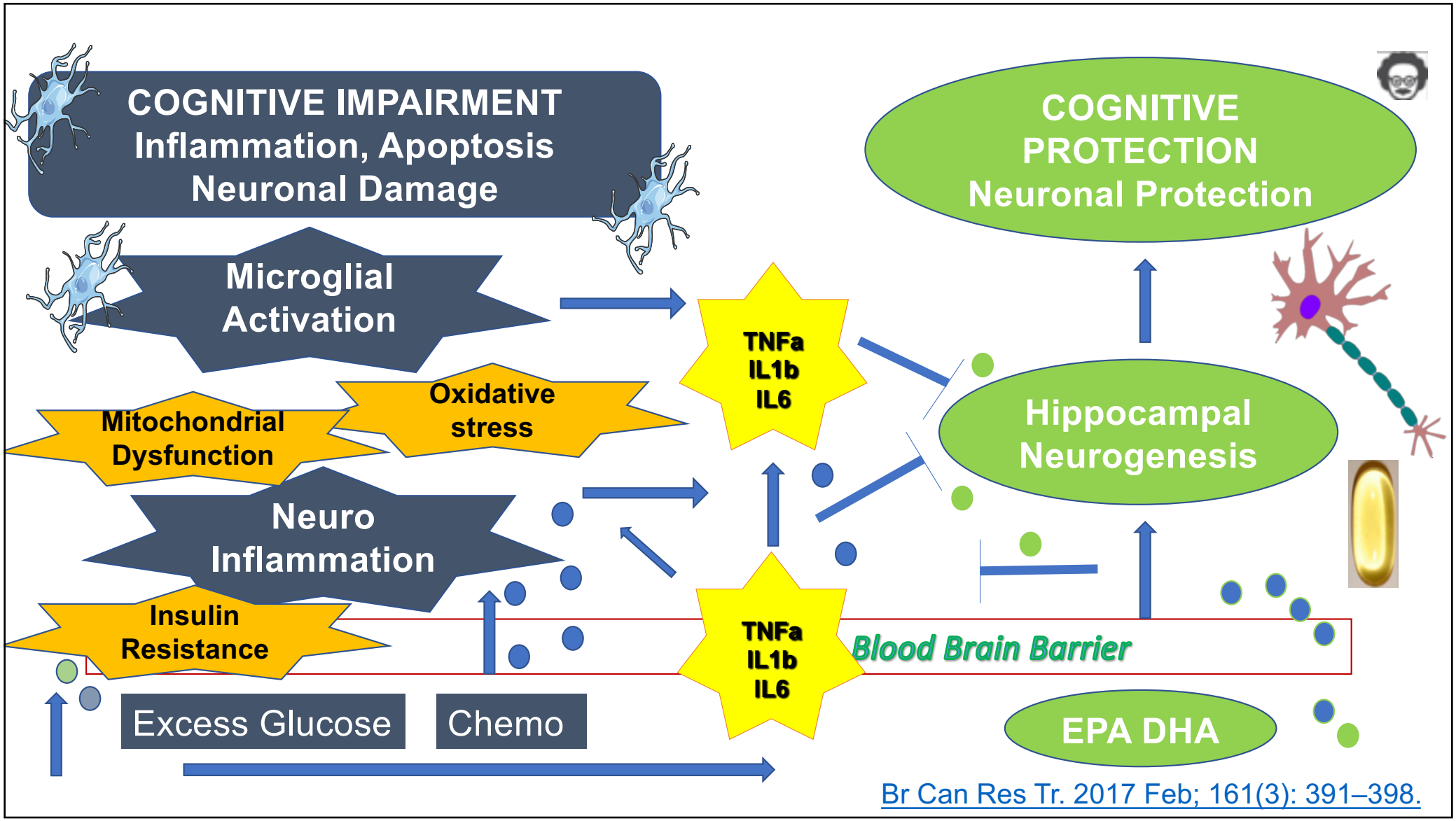
Genet Mol Res. 2014 Mar 24;13(1):2039-47. **Effects of curcumin on hippocampal expression of NgR and axonal regeneration in Aβ-induced cognitive disorder rats.** Yin HL, et al

Breast Cancer Research and Treatment Feb 2017, Vol 161, Iss 3, pp 391–398|

Clearing the fog: a review of the effects of dietary omega-3 fatty acids & added sugars on chemotherapy-induced cognitive deficits 1.8g/d

-Opposing actions of omega-3 fatty acids and added sugars on cognitive function, neuroinflammation, and adult hippocampal neurogenesis

-A diet rich in long-chain, marine-derived omega-3 fatty acids and low in added sugars may be an ideal pattern for preventing or alleviating neuroinflammation and oxidative stress, thereby protecting neurons from the toxic effects of chemotherapy.


COGNITIVE IMPAIRMENT
Inflammation, Apoptosis
Neuronal Damage
Microglial Activation
Oxidative stress
Mitochondrial Dysfunction
Neuro Inflammation
Insulin Resistance
Excess Glucose
Chemo
TNFa
IL1b
IL6
TNFa
IL1b
IL6
Blood Brain Barrier
COGNITIVE PROTECTION
Neuronal Protection
Hippocampal Neurogenesis
EPA DHA
Br Can Res Tr. 2017 Feb; 161(3): 391–398.

J Neurosci. 2010 Jul 21; 30(29): 9695–9707.

SIRT1 is essential for normal cognitive function and synaptic plasticity Shaday Michán,

SIRT1 localizes in the nuclei of neurons of the hippocampus

ACTIVATION OF SIRT I

- Resveratrol 1-5g/d (Stilbene)
- Berberine1.5-3 g/day (Isoquinoline alkaloid)
- Curcumin 2g-6g/day (Curcuminoids)
- Citicholine
- 250-1000 mg/day
- Melatonin 10-20mg hs
- Calorie Restriction
- Intermittent Fasting

RESVERATROL **1000mg bid x 52 weeks**

DBPCT: Resveratrol regulates neuro-inflammation and induces adaptive immunity in Alzheimer's disease

(BBB permeability)

Resveratrol decreases CSF MMP9, modulates neuro-inflammation, and induces adaptive immunity and SIRT1 activation. N=38

Nutrients. 2017 Jan 3;9(1). Effects of Resveratrol on Cognitiv
Performance, Mood and Cerebro Vascular Function i
Post-Menopausal Women;
A 14-Week Randomised Placebo-Controlled
Intervention Trial. (75 mg bid)

Significant improvements in the **performance of cognitive tasks : verbal memory** (p = 0.041),**overall cognitive performance** (p = 0.020), which correlated with **increase in CerebroVascular Responsiveness** (r = 0.327; p = 0.048). N=80

LION'S MANE MUSHROOM 3-5g/day
Hericium eranaceus (Yamabushitake)

- Strengthens Memory and Concentration
- Enhances Cognition
- Stimulates the synthesis of Nerve Growth Factor (NGF)
- Promotes and Accelerate Myelination (EDIBLE)

Phytother Res. 2009 Mar;23(3):367-72

LION's MANE **3-5 g/day**
Hericium eranaceus (Yamabushitake)
Cognitive Enhancement
Immune Modulation

Mori K et al **Improving effects of the mushroom Yamabushitake (Hericium erinaceus) on mild cognitive impairment: a double-blind placebo-controlled clinical trial.** Phytother Res. 2009 Mar;23(3):367-72. doi: 10.1002/ptr.2634.

Li K et al. **Protective effects of Hericium erinaceus mycelium and its isolated erinacine a against ischemia-injury-induced neuronal cell death via the inhibition of iNOS/p38 MAPK and nitrotyrosine.** *Int J Mol Sci*. 2014;15(9):15073–15089.

500-1000mg/d

Bacopa Monierri (Brahmi)

DBRCT n=84 over age 65 not taking medication 300-450mg per day x 90 days

- **Improved retention of new information**
- Decreased the rate of forgetting of newly acquired information
- There is evidence of an **antioxidant effect** of Brahmi in the **hippocampus.** (Bhattacharya et al. 2000).
- When combined with the finding of improved retention of information in this study, this suggests that the effect of the extract of Bacopa monniera may be mediated by antioxidant action within the hippocampus. N=76. p> 0.05

Neuropsychopharmacology (2002) 27, 279–281. **Chronic Effects of Brahmi (Bacopa monnieri) on Human Memory** Steven Roodenrys et al

Evid-Based Comp and Alt Med Vol 2012, Art ID 606424,10 pp

Effects of 12-Week **Bacopa monnieri** consumption on Attention, Cognitive Processing, Working Memory, and Functions of Both Cholinergic and Monoaminergic Systems in Healthy Elderly Volunteers Tatimah Peth-Nui, et al

double blind placebo controlled 60 adults 3 groups Crude extract BME **300mg or 600mg/**d or placebo No toxicity. Results: Both BME groups demonstrated **Enhanced attention, cognitive processing capability, working memory and cholinergic function**

Kiselev et al. BMC Cancer (2018) 18:904
https://doi.org/10.1186/s12885-018-4792-9

BMC Cancer

RESEARCH ARTICLE Open Access

A new promising way of maintenance therapy in advanced ovarian cancer: a comparative clinical study

Vsevolod I. Kiselev[1], Levon A. Ashrafyan[2], Ekaterina L. Muyzhnek[3*], Evgeniya V. Gerfanova[2], Irina B. Antonova[2], Olga I. Aleshikova[2] and Fazlul H. Sarkar[4]

Abstract

Background: There is an urgent need for more novel and efficacious therapeutic agents and strategies for the treatment of ovarian cancer - one of the most formidable female malignancies. These approaches should be based on comprehensive understanding of the pathobiology of this cancer and focused on decreasing its recurrence and metastasis. The aim of this study was to evaluate the efficacy of five-year maintenance therapy with indole-3-carbinol (I3C) as well as I3C and epigallocatechin-3-gallate (EGCG) conducted before, during, and after combined treatment compared with combined treatment alone in advanced ovarian cancer.

Methods: Patients with stage III-IV serous ovarian cancer were assigned to receive combined treatment plus I3C (arm 1), combined treatment plus I3C and EGCG (arm 2), combined treatment plus I3C and EGCG plus long-term platinum-taxane chemotherapy (arm 3), combined treatment alone without neoadjuvant platinum-taxane chemotherapy (control arm 4), and combined treatment alone (control arm 5). Combined treatment included neoadjuvant platinum-taxane chemotherapy, surgery, and adjuvant platinum-taxane chemotherapy. The primary endpoint was overall survival (OS). Secondary endpoints were progression-free survival (PFS) and rate of patients with recurrent ovarian cancer with ascites after combined treatment.

Results: After five years of follow-up, maintenance therapy dramatically prolonged PFS and OS compared to control. Median OS was 60.0 months (95% CI: 58.0–60.0 months) in arm 1, 60.0 months (95% CI: 60.0–60.0 months) in arms 2 and 3 while 46.0 months (95% CI: 28.0–60.0 months) in arm 4, and 44.0 months (95% CI: 33.0–58.0 months) in arm 5. Median PFS was 39.5 months (95% CI: 28.0–49.0 months) in arm 1, 42.5 months (95% CI: 38.0–49.0 months) in arm 2, 48.5 months (95% CI: 39.0–53.0 months) in arm 3, 24.5 months (95% CI: 14.0–34.0 months) in arm 4, 22.0 months (95% CI: 15.0–26.0 months) in arm 5. The rate of patients with recurrent ovarian cancer with ascites after combined treatment was significantly less in maintenance therapy arms compared to control.

Conclusions: Long-term usage of I3C and EGCG may represent a new promising way of maintenance therapy in advanced ovarian cancer patients, which achieved better treatment outcomes.

Trial registration: Retrospectively registered with ANZCTR number: ACTRN12616000394448. Date of registration: 24/03/2016.

Keywords: Ovarian cancer, Survival, Maintenance therapy, Indole-3-carbinol, Epigallocatechin-3-gallate

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Background

Ovarian cancer (OC) has long been one of the most difficult and treacherous female cancers, accounting for nearly 150,000 lethal cases annually worldwide [1]. Various estimates put five-year overall survival with advanced OC at 12–42%. Maximal cytoreductive surgery, followed by platinum-taxane chemotherapy (TP and TC regimens) has been standard treatment of OC since 1996. However, 60–80% of such patients relapse in six to 24 months, which requires further chemotherapy and eventually makes the tumor chemoresistant. The relapse with chemoresistant tumors results in grievous complications (ileus, ascites, cachexia) leading to early death.

More effective OC treatment strategies are urgently required to improve survival. They should obviously be focused on minimizing recurrence rate and metastasis and overcoming drug resistance. Accumulating evidence suggests that it cannot be done solely with special regimens of standard chemotherapy [2–4], or a combination of conventional chemotherapy and monotargeted antitumor drugs [5–8]. Targeted antitumor drugs used in a maintenance therapy regimen have recently gained increasing attention as a promising management option for recurrent OC, helping to extend progression-free intervals [9–13].

Since the mid-1990s, a new theory behind the nature of cancer has been steadily gaining traction, namely that of a dominating role of cancer stem cells (CSCs), also known as 'cancer-initiating cells' or 'tumor-initiating cells,' a special rare population of immortal aggressive tumorigenic cells capable of self-renewal and pluripotency. There is a huge array of evidence suggesting that CSCs resistant to conventional chemo- and radiotherapy are responsible for cancer initiation, progression, metastasis, and recurrence, as well as radio- and drug resistance [14–16]. Superior CSCs resistance to anti-cancer drugs is explained biologically by their hyperexpression of multidrug efflux transporters, antiapoptotic factors, and DNA repair and detoxifying enzymes [16–18].

The concept of cancer stem cells has been proven both experimentally and clinically in many cancers, including OC [19, 20]. Ovarian CSCs were confirmed to play a big role in the development of chemoresistance and generation of recurrent and metastatic foci in OC [21, 22].

Search for and development of drugs inhibiting CSCs is a new unfolding opportunity for targeted antitumor therapy, which can affect the current paradigm of anti-cancer drug development in general. Over the last decade, a lot of work has been done to develop new drugs to target CSCs. There are four known groups of molecular targets for anti-CSCs therapy: 1) cell-surface molecular markers of CSCs; 2) proteins of various signaling pathways, controlling CSCs survivability and differentiation; 3) membrane transporters crucial for CSCs anticancer multidrug resistance, and 4) CSCs cellular microenvironment ("niche") molecular factors [16, 17]. Some of the newly identified compounds that selectively target CSCs have been evaluated in preclinical and clinical studies [17]. Within the broader context of improving the overall suffering and survival of oncological patients, such selective CSCs inhibitors are suggested for concomitant use with conventional chemotherapeutic drugs whose important role is to eliminate bulk tumor cells [23].

Our comparative clinical trial investigated the efficacy of long-term maintenance therapy with indole-3-carbinol (I3C) as well as maintenance therapy with I3C and epigallocatechin-3-gallate (EGCG), agents demonstrating multiple antitumor activities, including specifically the inhibition of CSCs. The current study enrolled untreated advanced OC patients.

Methods

Patient population

All eligible women were ≥ 39 years of age with histologically confirmed International Federation of Gynecology and Obstetrics (FIGO) stage III to IV serous epithelial OC (serous carcinoma) defined as high-grade (Grade III) serous carcinoma according to the WHO grading system [24].

Eligible patients also met the following criteria: Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2; adequate hematologic, hepatic, and renal functions: absolute granulocyte count ≥ $1.5 \times 10^3/mm^3$; platelets ≥ $100 \times 10^3/mm^3$; bilirubin, creatinine within normal limits; aspartate aminotransferase (AST) and alanine aminotransferase (ALT) < 2.0 times normal upper limit; AST and ALT < 5.0 times normal upper limit if liver metastases present; absence of significant comorbidities (documented history of gastric/duodenal ulcer or heart attack within the last 12 months; polyneuropathy; decompensated diabetes), and submission of written informed consent.

Ineligibility criteria included *BRCA* genes mutations, malignancies of other localizations, positive RW or HIV tests, alcohol or drug abuse, pregnancy or lactation, logistical issues (remote residence etc.), or any uncontrolled psychiatric illnesses or conditions potentially hampering compliance and/or monitoring, other severe comorbidities potentially (investigator discretion) affecting the patient's ability to participate in the trial.

All study procedures (the study protocol) were approved by the local Ethics Committee of the Federal State Budgetary Institution "Russian Scientific Center of Roentgenoradiology" (RSCRR) of the Ministry of Healthcare of the Russian Federation and conducted in accordance with the principles of Good Clinical Practice and Declaration of Helsinki. All patients submitted written informed consent at the time of enrollment.

Peritoneal cancer index (PCI) was determined for all patients in the study at screening using data obtained by

thoracoabdominal computed tomography to assess the initial tumor spread [25].

All required procedures were carried out by the same surgical team.

Study design and treatment

To provide maintenance therapy effect estimates, the original plan was to enroll 300 patients, with 60 patients per arm. The target sample size ($n = 300$) was also determined by the number of eligible patients at RSCRR during 5-year period of patient enrollment from January 2004 through December 2009.

According to the initial protocol, patients were to be randomly assigned to receive combined treatment plus I3C continuously (arm 1), combined treatment plus I3C and EGCG continuously (arm 2), combined treatment plus I3C and EGCG continuously plus long-term platinum-taxane chemotherapy (arm 3), combined treatment alone without neoadjuvant chemotherapy (arm 4), and combined treatment alone (arm 5). In the process of enrollment, it turned out to be problematic to get written consent to randomization from enough advanced OC patients to complete five arms balanced by the number of patients. So the decision was made, after discussion with the RSCRR ethics committee, that patients should be enrolled on the basis of treatment preference (patients' choice). The trial protocol was modified accordingly. As a result, 284 patients were enrolled in January 2004 through December 2009 at RSCRR and treated in accordance with their choice made at the moment of diagnosis (arm 1, $n = 46$; arm 2, $n = 76$; arm 3, $n = 42$; arm 4, $n = 40$; arm 5, $n = 80$). Hofmann MA et al. [26] earlier described a similar enrollment issue in a clinical study of advanced melanoma, with the same solution.

According to the modified protocol, all enrolled patients were offered to choose from five treatment options: combined treatment plus twice daily oral administration of 200 mg of I3C continuously (arm 1), combined treatment plus twice daily oral administration of 200 mg of I3C and 200 mg of EGCG continuously (arm 2), combined treatment plus twice daily oral administration of 200 mg of I3C and 200 mg of EGCG continuously plus long-term platinum-taxane chemotherapy, 2–3-month cycles (arm 3), combined treatment alone without neoadjuvant chemotherapy (arm 4), and combined treatment alone (arm 5) (Fig. 1). Combined treatment included neoadjuvant chemotherapy (NACT) consisting of two to four three-week cycles of TP regimen (1st day: intravenous paclitaxel 175 mg/m^2 with premedication; 2nd day: intravenous cisplatin 75–100 mg/m^2 with hyperhydration) or TC regimen (1st day: intravenous paclitaxel 175 mg/m^2 with premedication; 2nd day: intravenous carboplatin AUC 5), primary surgery (panhysterectomy with subtotal resection of the greater omentum and the maximum removal of disseminated tumor foci), carried out 28 days after the last cycle of NACT, and postoperative adjuvant chemotherapy (ACT) consisted of five to six 3-week cycles of TP or TC regimen performed 14 days after surgery. Platinum-taxane chemotherapy TP and TC regimen were distributed almost evenly in each arm.

Patients in combined treatment arms 1, 2, 3, and 5 had a high perioperative risk profile or a low likelihood of achieving cytoreduction to < 1 cm of residual disease (ideally to no visible disease). Thus, the combined treatment with NACT was conducted in these arms according to generally accepted international treatment guidelines [27, 28] as well as to Russian Federation treatment guidelines and local RSCRR treatment guidelines for advanced OC. In accordance with RSCRR treatment guidelines for FIGO III-IV OC (Protocol № C56/10, order № 80-o dated 17.08.2010), a large volume of ascitic fluid in the abdomen and CA-125 level more than 500 U/ml are additional criteria for unresectability by primary debulking and presurgery NACT. At screening, the rates of patients with ascites in all arms were about 70% and PCI medians were from 24 to 29 (Table 1). It was shown earlier that PCI > 10 was positively associated with a poor prognosis for any intra-abdominal and intrapelvic malignant tumor with peritoneal spread, including advanced OC [25, 29].

The efficacy of NACT was evaluated by CA-125 level dynamics according to the Rustin criterion [30] and by tumor response per RECIST criteria [31]. Clinical manifestations of NACT success were the disappearance of ascites, reduction of tumor foci size, their smaller dissemination that allowed to perform the subsequent surgical operation as completely as possible and to reduce the risk of postoperative complications. The number of NACT cycles (from two to four) depended on time to CA-125 ≤ 35 U/mL, general declining profile of CA-125, general condition, and laboratory and diagnostic data.

The efficacy of ACT was estimated per RECIST criteria [31] in 21 days after the end of the last ACT cycle. The number of ACT cycles (five or six) depended on personal clinical and laboratory characteristics of every patient, namely, residual tumor size, CA-125 level, general condition, and laboratory and diagnostic data.

Maintenance therapy with I3C as well as maintenance therapy with I3C and EGCG started 14 days prior to combined treatment and continued through combined treatment and for 5 years of the follow-up period.

I3C is the active substance of medical drug Indinol® Forto, capsules, 200 mg I3C per capsule (MiraxBioPharma, Joint-Stock Company, Russia) [32]. I3C (100 mg per capsule) and EGCG (100 mg per capsule) are the active components of dietary supplement Promisan® (MiraxBioPharma, Joint-Stock Company, Russia) [33].

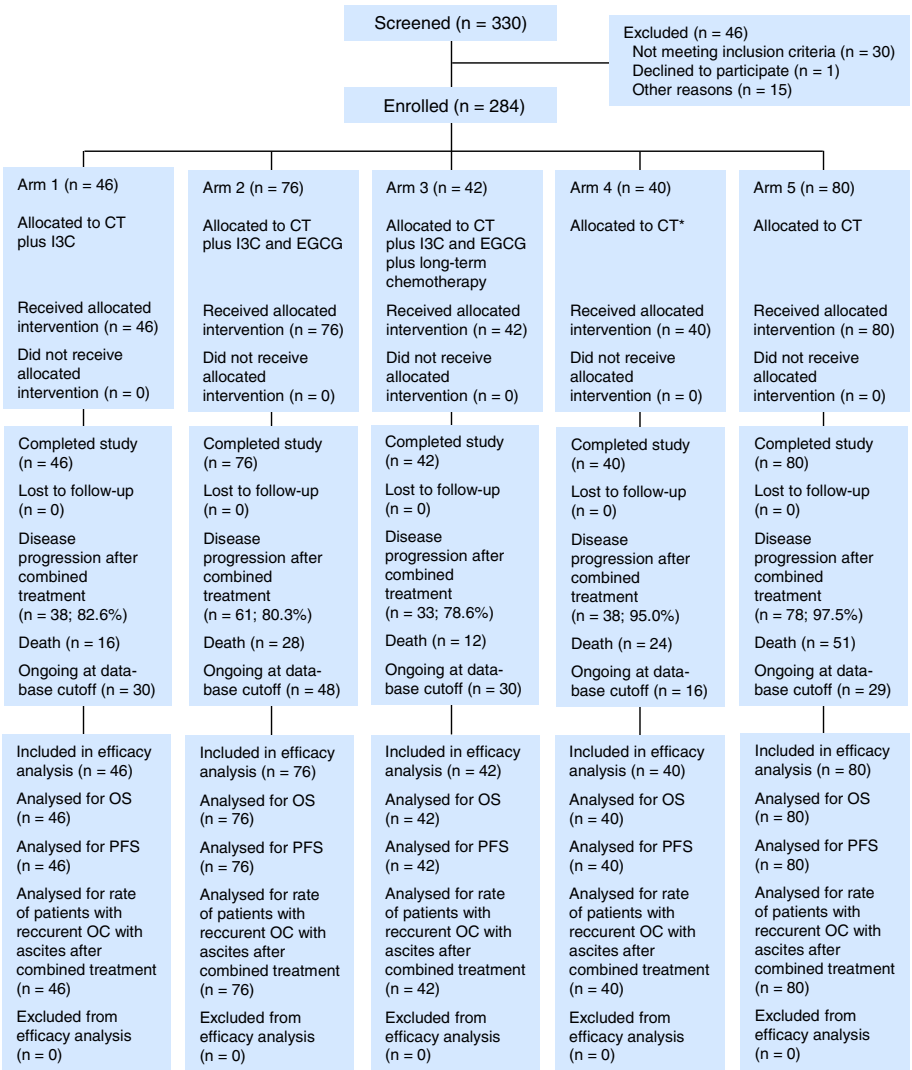

Fig. 1 CONSORT diagram. *CT* combined treatment with neoadjuvant chemotherapy; *CT** combined treatment without neoadjuvant chemotherapy; *OS* overall survival; *PFS* progression-free survival; *OC* ovarian cancer

If the disease progressed (growth of existing or verification of new OC foci), patients were recommended to undergo chemotherapy as per approved protocol, depending on the length of the platinum-free interval (date of last platinum administration to date of progression). If an OC patient relapsed but background factors were beneficial (no ascites, complete cytoreductive surgery, long platinum-free interval, and general satisfactory status), a possibility for secondary debulking surgery was considered. Patients for secondary debulking surgery were selected on the basis of the AGO score developed and validated in DESKTOP I/II trials [34, 35].

Study endpoints

The primary endpoint was overall survival (OS) defined as the interval between the date of diagnosis and the date of death from any cause. The first secondary endpoint was progression-free survival (PFS) defined as time from random assignment to disease progression per RECIST, clinical progression (per investigator) or CA-125 progression (per GCIG criteria), or death from any cause. The second secondary endpoint was the rate of patients with recurrent OC with ascites after combined treatment within 5 years of follow-up.

Efficacy and toxicity assessment

Primary efficacy analyses included all the intent-to-treat patients. Positron emission tomography-computed tomography (PET-CT) or magnetic resonance imaging (MRI) was performed at baseline and every 3 months throughout the study period. Ultrasonography was performed every month during year 1, and then at least

Table 1 Patient demographic and clinical characteristics

Characteristic	Arm 1 ($n = 46$)	Arm 2 ($n = 76$)	Arm 3 ($n = 42$)	Arm 4 ($n = 40$)	Arm 5 ($n = 80$)
Age, years					
Median	54.0	54.0	54.5	54.2	54.1
Range	40–76	43–71	41–68	47–68	39–69
Ethnicity, No. (%)					
White	42 (91.3)	68 (89.5)	38 (90.5)	36 (90)	73 (91.2)
Asian	4 (8.7)	7 (9.2)	4 (9.5)	3 (7.5)	6 (7.5)
Black	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Other	0 (0)	1 (1.3)	0 (0)	1 (2.5)	1 (1.2)
FIGO stage at screening, No. (%)					
III	38 (82.6)	60 (78.9)	34 (80.9)	32 (80.0)	66 (82.5)
IV	8 (17.4)	16 (21.1)	8 (19.0)	8 (20.0)	14 (17.5)
PCI					
Median	24	27	27	27	29
Range	9–36	8–37	7–37	7–37	7–37
7–10 (≤ 10), No. (%)	2 (4.3)	4 (5.3)	4 (9.5)	2 (5.0)	2 (2.5)
11–20	12 (26.1)	20 (26.3)	8 (19.0)	8 (20.0)	20 (25.0)
21–30	23 (50.0)	26 (34.2)	14 (33.3)	17 (42.5)	26 (32.5)
31–37	9 (19.6)	26 (34.2)	16 (38.1)	13 (32.5)	32 (40.0)
ECOG performance status at screening, No. (%)					
0	40 (87.0)	67 (88.2)	37 (88.1)	34 (85.0)	69 (86.3)
1	3 (6.5)	5 (6.6)	3 (7.1)	4 (10.0)	6 (7.5)
2	3 (6.5)	4 (5.3)	2 (4.8)	2 (5.0)	5 (6.3)
p[a]	0.96	0.84	0.86	0.93	
Rate of patients with ascites					
at screening[b], No. (%)	31 (67.4)	51 (67.1)	29 (69.0)	28 (70.0)	55 (68.8)
95% CI	52–80	55–68	53–82	54–83	57–79
p[b]	0.87	0.82	0.97	0.89	
Standard chemotherapy regimen, No. (%)					
TP	26 (57)	40 (53)	20 (48)	18 (45)	37 (46)
TC	20 (43)	36 (47)	22 (52)	22 (55)	43 (54)
CA-125 level, U/mL					
at screening					
Mean	579.78	584.32	581.85	581.98	583.75
Range	110- > 600	115- > 600	120- > 600	110- > 600	105- > 600
at presurgery					
Mean ± SD[c]	31.50 ± 5.19	37.91 ± 21.43	42.26 ± 24.50	581.98 ± 85.07	68.70 ± 16.23
Range	25–45	30–210	30–190	69- > 600	35–110
after combined treatment					
Mean ± SD[c]	12.78 ± 2.78	10.42 ± 4.07	12.67 ± 5.48	31.05 ± 8.70	32.44 ± 6.23
Range	10–20	8–42	8–35	20–54	20–55
Primary debulking surgery at combined treatment[d], No. (%)					
Complete cytoreduction (no visible tumor foci)	39 (84.8)	63 (82.9)	34 (81.0)	5 (12.5)	20 (25.0)
Optimal cytoreduction (≤ 1 cm)	7 (15.2)	13 (17.1)	8 (19.0)	21 (52.5)	51 (63.8)

Table 1 Patient demographic and clinical characteristics *(Continued)*

Characteristic	Arm 1 ($n = 46$)	Arm 2 ($n = 76$)	Arm 3 ($n = 42$)	Arm 4 ($n = 40$)	Arm 5 ($n = 80$)
Suboptimal cytoreduction (> 1 cm)	0 (0)	0 (0)	0 (0)	14 (35.0)	9 (11.3)
Disease progression (tumor recurrence rate) after combined treatment within five years of follow-up, No. (%)	38 (82.6)	61 (80.3)	33 (78.6)	38 (95.0)	78 (97.5)
Rate of patients without recurrent ovarian cancer within five years of follow-up, No. (%)	8 (17.4)	15 (19.7)	9 (21.4)	2 (5.0)	2 (2.5)

FIGO International Federation of Gynecology and Obstetrics, *PCI* peritoneal cancer index, *ECOG* Eastern Cooperative Oncology Group, *95% CI* 95% confidence interval, *SD* standard deviation

[a]Mann-Whitney U-test was applied to determine the differences between arms 1–4 vs arm 5

[b]Chi-square criterion was applied to determine the differences between arms 1–4 vs arm 5

[c]Student's test was applied to determine mean level, standard deviation, and the differences between arms 1–3 vs arm 5

All differences between arms 1–3 vs arm 5 were statistically significant ($p < 0.0001$)

[d]Mann-Whitney U-test was applied to compare the degree of surgery used in arms 1–3 vs arm 5. Degrees of surgery were scored as follows: macroscopic completed resection (no visible tumor foci) – 0, optimal debulking (≤ 1 cm) – 1, suboptimal debulking (> 1 cm) – 2. All differences between arms 1–3 vs arm 5 were statistically significant ($p < 0.0001$)

every 3 to 4 months during years 2–3 and every 6 months during years 4–5. CA-125 test was performed by a local laboratory monthly during the study.

Disease recurrence was defined as an objective clinical diagnosis based on PET-CT and MRI, ultrasonography, physical, or pathological findings. Ascites was detected using ultrasonography, tomographic studies, and intraoperative findings.

Performance status (PS) was measured using ECOG criteria at screening, after combined treatment, and at the end of the study after 5 years of follow-up.

Quality of life (QOL) was assessed at screening, after combined treatment, and at the end of the study after 5 years of follow-up using the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire-C30, version 3.0. The scales and items of the questionnaire were transformed to a scale of 0–100, using a scoring manual [36]. Evaluation of Global health status, Functional status, and assessment of side effects of the treatment (Symptom scales) was conducted. The Functional scales contained questions about the physical, emotional, cognitive, and social functions. The Symptom scales contained questions about side effects of treatment, such as fatigue, nausea, vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties. A high score on a Functional scales or Global health status implies good functioning or high QOL, whereas a high score on a Symptom scales indicates a high degree of complaints or disturbance.

Adverse events were monitored continuously and evaluated using National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0 [37].

Statistical analysis

The planned enrollment of 300 patients ($n = 60$ patients per arm) was selected to generate maintenance therapy effect estimates. As a result, 284 patients were enrolled in January 2004 through December 2009 at RSCRR and treated in accordance with their choice made at the moment of diagnosis (arm 1, $n = 46$; arm 2, $n = 76$; arm 3, $n = 42$; arm 4, $n = 40$; arm 5, $n = 80$), according to the modified protocol.

OS and PFS were estimated by Kaplan-Meier analysis [38] and expressed as median value with corresponding 95% confidence interval (95% CI) and 25th, 75th percentiles. Pearson's correlation coefficients between PFS and OS for all the arms were also calculated.

Multivariate analysis for PFS and OS was performed using Cox proportional hazards model [39]. Hazard ratio (HR), 95% CI, and p-value were calculated for the factors likely to influence the survival rate. The PCI cutoff values were determined on the basis of receiver operator characteristic (ROC) curves.

Chi-square test (χ^2 test) was applied to determine the statistical significance of differences between rates of patients with and without ascites in different arms after combined treatment within 5 years of follow-up, with 95% CIs to be calculated by Klopper-Pearson method. Mann-Whitney U-test, Chi-square test (χ^2 test), and Student's t-test were used to estimate the significance of inter-arm differences in other indicators.

Data were analyzed using Statistica package version 10.0 (StatSoft Inc., USA). The Bonferroni correction was used as appropriate to eliminate the multiple comparisons effect. Multivariate analysis was carried out using SPSS statistical software program, version 20.0 (SPSS Inc., Chicago, IL, USA). For all tests, p-value < 0.05 was taken as the critical level of significance.

Results

Patients

Of 330 eligible screened women with advanced OC, 284 were enrolled between January 2004 and December 2009 at RSCRR and distributed into three maintenance therapy arms and two control arms (arm 1, $n = 46$; arm 2, $n = 76$; arm 3, $n = 42$; arm 4, $n = 40$; arm 5, $n = 80$).

Baseline demographic and clinical characteristics were well balanced between treatment arms (Table 1).

Documented CA-125 level - a widely used marker of response in OC trials - at screening was similar among the treatment arms. Further, at presurgery and after completion of combined treatment (after the last course of ACT), CA-125 readings demonstrated a statistically significant benefit to maintenance therapy arms 1–3 compared with control arm 5 ($p < 0.0001$) (Table 1). At presurgery the mean CA-125 level in arm 1 equalled or was less than the threshold CA-125 value (31.50 ± 5.19 U / ml). CA-level in arms 2 and 3 was a little higher than the normal value and was in so-called "grey scale" (37.9 ± 21.43 U / ml and 42.26 ± 24.5 U / ml, respectively) in comparison with control arm 5 without maintenance therapy (68.70 ± 16.23 U / ml (Table 1). CA-125 level in control arm 4 without NACT remained still high (581.98 ± 85.07 U / ml).

Importantly, the vast majority of patients (81–85%) from maintenance therapy arms 1–3 had undergone successful complete cytoreduction as primary debulking surgery, in which all visible tumor foci were removed ($p < 0.0001$). At presurgery moment, patients from arms 1–3 had taken I3C and EGCG agents for 14 days prior to NACT, during NACT, and for a time between the last NACT cycle and surgery. Other patients in arms 1–3 (15–19%) were optimally debulked to ≤ 1 cm. At the same time most patients in control arms 4 and 5 could not be subjected to complete cytoreduction because of lack of technical possibility for such surgery, and so they were optimally debulked to ≤ 1 cm and suboptimally debulked to > 1 cm (Table 1).

Efficacy

At the time of efficacy analysis, 5 years after combined treatment commencement for the last enrolled patient, 16 patients in arm 1, 28 in arm 2, 11 in arm 3, 19 in arm 4, and 51 in arm 5 had experienced an OS event, while 38 patients in arm 1, 61 in arm 2, 33 in arm 3, 38 in arm 4, and 78 in arm 5 had experienced a PFS event.

Median OS in arms 1–3 was 60.0 months, compared with 46.0 months and 44.0 months in control arms 4 and 5, respectively. Median OS in arms 2+3 (patients receiving I3C and EGCG) was 60.0 months compared with median OS 44.0 months in control arms 4+5 (Fig. 2a, c; Table 2). Median PFS in arm 1 was 39.5 months, in arm 2 – 42.5 months, in arm 3 – 48.5 months, in arm 4 – 24.5 months, in arm 5 – 22.0 months. Median PFS in arms 2+3 was 44.0 months and in control arms 4+5 was 23.0 months (Fig. 2b, d; Table 2).

Pearson's correlation coefficients between PFS and OS for arms 1–5 were respectively 0.811, 0.874, 0.805, 0.565 and 0.711, while for arms 2+3 and arms 4+5, respectively, 0.855 and 0.661 ($p < 0.05$) (Table 2).

Multivariate survival analysis performed using Cox proportional hazards model indicated that maintenance therapy with I3C, maintenance therapy with I3C and EGCG, PCI ≤ 25, and FIGO stage III were independent favorable prognostic factors statistically significantly influencing both OS and PFS ($p < 0.0001$ for all above variables) in advanced OC patients. NACT application and secondary debulking surgery at time of relapse did not have prognostic statistical significance both for OS ($p = 0.246$, $p = 0.930$, respectively) and PFS ($p = 0.521$, $p = 0.205$, respectively) (Table 3). Therefore, in this study maintenance therapy with I3C as well as maintenance therapy with I3C and EGCG were the factors significantly associated with survival in advanced OC patients, after adjustment for such variables as neoadjuvant chemotherapy application, initial tumor spread (PCI), FIGO stage III or IV, and secondary surgery at time of relapse.

After combined treatment within the five-year follow-up period, patients receiving maintenance therapy with I3C as well as maintenance therapy with I3C and EGCG demonstrated a dramatic decrease in ascites OC recurrences: 8 to 9% in arms 1–3 and 8.5% in arms 2+3, vs 60 and 63% in control arms 4 and 5, respectively, and 61% in control arms 4+5 (Table 2). In any comparative combinations, all differences between maintenance therapy arms and control arms were statistically significant ($p < 0.0001$). The total tumor recurrence rate with and without ascites after combined treatment in arms 1–5 was respectively: 82.6%, 80.3%, 78.6%, 95.0%, and 97.5% (Fig. 1, Table 1). The rate of patients without OC recurrences within 5 years of follow-up in arms 1–5 was respectively: 17.4%, 19.7%, 21.4%, 5.0%, and 2.5% (Table 1).

Performance status, quality of life and adverse events

ECOG PS score at screening was similar in all the five arms (Table 1), with important statistically significant improvements demonstrated in maintenance therapy arms compared to control in five-year follow-up, 83–88% of surviving patients from arms 1–3 having ECOG scores from 0 to 2, compared to only 55–56% in control arms 4 and 5 (Table 4).

The trend was the same in QOL comparative assessments using the EORTC QLQ-C30 questionnaire. All the results on EORTC QLC-C30 performed at baseline, after combined treatment, and at the end of the study are summarized in Tables 5, 6 and 7. While at screening there was no statistically significant difference in EORTC QLC-C30 scores between maintenance therapy arms and control arm 5, the former demonstrated statistically significant improvements in Global Health Status and Functional Status after 5 years of follow-up. Importantly, arm 3 patients, despite being subject to long-term chemotherapy, reported the same elevated Functional Status as compared to control arm 5 as arm 2 patients

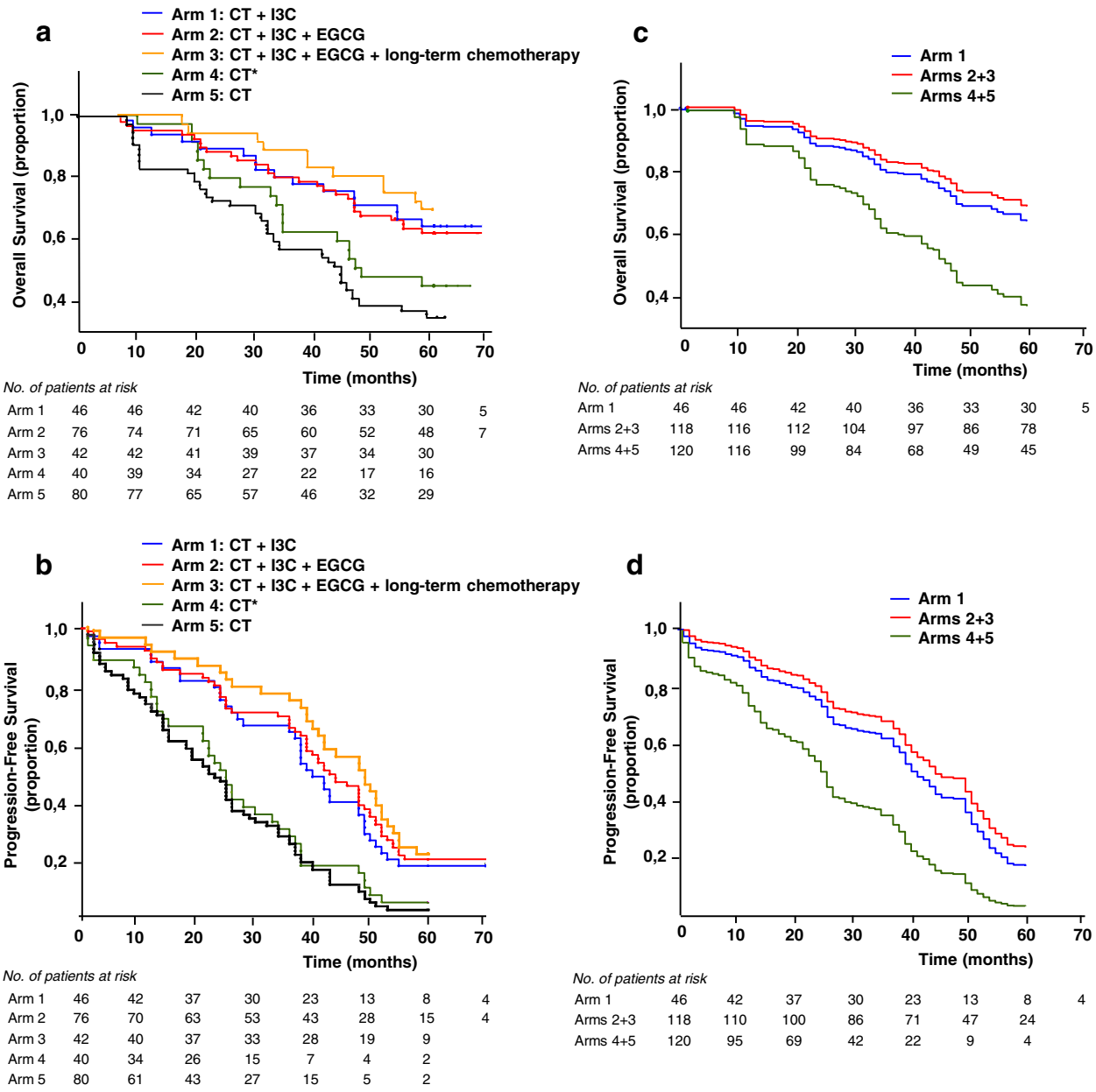

Fig. 2 Kaplan–Meier analysis of OS (**a, c**) and PFS (**b, d**) in ovarian cancer patients. Advanced ovarian cancer patients receiving CT plus I3C continuously (arm 1), CT plus I3C and EGCG continuously (arm 2), CT plus I3C and EGCG continuously plus long-term platinum-taxane chemotherapy, 2–3-month cycles (arm 3), CT* alone (arm 4), CT alone (arm 5). *OS* overall survival, *PFS* progression-free survival, *I3C* indole-3-carbinol, *EGCG* epigallocatechin-3-gallate, *CT* combined treatment with neoadjuvant platinum-taxane chemotherapy, *CT** combined treatment without neoadjuvant platinum-taxane chemotherapy

who were under the same I3C and EGCG regimen but without the long-term chemotherapy.

In this study, the administration of I3C and EGCG did not negatively affected patients' general condition and did not cause any additional adverse events (AEs) beyond the AEs caused by the administration of standard chemotherapy drugs (Table 8). All reported treatment-related AEs were stopped independently or by symptomatic therapy. There were no AEs requiring reduction in standard chemotherapy dosages or any changes in the regimen of standard and/or maintenance therapy. There were no cases of discontinuing, or changing the recommended dosages of I3C- and EGCG-containing drugs. There were no treatment-related deaths.

Discussion

Ovarian cancer, also known colloquially among oncologists as the "Silent Killer," still presents a formidable

Table 2 Maintenance therapy efficacy analysis

	Arm 1	Arm 2	Arm 3	Arms 2+3	Arm 4	Arm 5	Arms 4+5
	CT + I3C 400 mg	CT + I3C 400 mg + EGCG 200 mg	CT + I3C 400 mg + EGCG 200 mg + long-term chemotherapy	CT + I3C 400 mg + EGCG 200 mg	CT*	CT	CT**
	(*n* = 46)	(*n* = 76)	(*n* = 42)	(*n* = 118)	(*n* = 40)	(*n* = 80)	(*n* = 120)
Primary end point: OS[a]							
Deaths, No. (%) Kaplan-Meier OS time, months	16 (34.8)	28 (36.8)	12 (28.6)	40 (33.9)	24 (60.0)	51 (63.8)	75 (62.5)
Median	60	60	60	60	46	44	44
95% CI	58–60	60–60	60–60	60–60	28–60	33–58	34–54
Q1	47	45	58	47	21.5	22	22
Q3	62	60	60	60	60	60	60
Secondary end point: PFS per RECIST, clinical progression, CA-125 progression, or death[b]							
Kaplan-Meier PFS time, months							
Median	39.5	42.5	48.5	44	24.5	22	23
95% CI	28–49	38–49	39–53	40–49	14–34	15–26	19–26
Q1	24	24.5	36	25	12.5	10.5	11.5
Q3	51	54	55	55	37.5	36.5	37
r,	0.811	0.874	0.805	0.855	0.565	0.711	0.661
Secondary end point: Rate of patients with recurrent OC with ascites after combined treatment							
No. (%)	3 (7.9)	5 (8.2)	3 (9.1)	8 (8.5)	24 (63.2)	47 (60.3)	71 (61.2)
95% CI, %	1.7–21.4	2.7–18.1	1.9–24.3	3.7–16.1	46.0–78.2	48.5–71.2	51.7–70.1
Rate of patients with recurrent OC without ascites after combined treatment							
No. (%)	35 (92.1)	56 (91.8)	30 (90.9)	86 (91.5)	14 (36.8)	31 (39.7)	45 (38.8)
95% CI, %	78.6–98.3	81.9–97.3	75.7–98.1	83.9–96.3	21.8–54.0	28.8–51.5	29.9–48.3
p^c	< 0.0001	< 0.0001	< 0.0001		0.7634		
p^d				< 0.0001			

CT combined treatment with neoadjuvant chemotherapy, *CT** combined treatment without neoadjuvant chemotherapy, *CT*** combined treatment with and without neoadjuvant chemotherapy, *I3C* indole-3-carbinol, *EGCG* epigallocatechin-3-gallate, *OS* overall survival, *PFS* progression-free survival, *95% CI* 95% confidence interval, *Q1* 25th percentile, *Q3* 75th percentile, *r* Pearson's correlation coefficient between OS and PFS ($p < 0.05$), *OC* ovarian cancer

[a]Defined as the time from the date of diagnosis to the date of death from any causes. At the time of this analysis, 30 patients in arm 1, 48 patients in arm 2, 31 patients in arm 3, 21 patients in arm 4, 29 patients in arm 5 were censored

[b]Defined as the time from random assignment to disease progression per RECIST, clinical progression (per investigator) or CA-125 progression (per GCIG criteria), or death from any causes. At the time of this analysis, 8 patients in arm 1, 15 patients in arm 2, 9 patients in arm 3, 2 patients in arm 4, 2 patients in arm 5 were censored

[c]Chi-square criterion was applied to determine the differences between arms 1–4 vs arm 5

[d]Chi-square criterion was applied to determine the difference between arms 2+3 vs arms 4+5

challenge. This malignancy remains associated with high rates of morbidity and mortality because it is largely asymptomatic in the early stages, which leads to late diagnosis, while the tumor itself is prone to broad early dissemination, active metastasis, and multidrug resistance emerging after chemotherapy.

A great deal of effort is made to improve current conventional treatment of OC. Some interesting promising approaches obtaining encouraging results to manage recurrent OC became known during last years, such as hyperthermic intraperitoneal intraoperative chemotherapy following secondary cytoreduction in recurrent platinum-sensitive OC patients [40, 41]. However, the medical community is not yet in a position to state that, in general, enhancements of conventional treatment methods or combined usage of conventional chemotherapy with modern monotargeted antitumor drugs have translated into tangible and significant progress in improving the outcomes of OC patients [5–8, 42, 43]. Apparently, the main cause of this failure is insufficient and incomprehensive understanding of the cellular and molecular biology of heterogeneous chemoresistant and recurrent ovarian tumors.

In recent years, OC has repeatedly and strongly been described as a cancer stem cell disease [19, 20, 44–47]. Ovarian CSCs were found experimentally in vitro and in

Table 3 Adjusted overall survival and progression-free survival of patients by multivariate Cox regression analyses

Variables	OS		PFS	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Neoadjuvant chemotherapy	1.367 (0.806–2.319)	0.246	1.136 (0.770–1.678)	0.521
Maintenance therapy with I3C	0.272 (0.147–0.502)	**< 0.0001**	0.309 (0.202–0.472)	**< 0.0001**
Maintenance therapy with I3C and EGCG	0.244 (0.150–0.396)	**< 0.0001**	0.241 (0.172–0.339)	**< 0.0001**
PCI (> 25 vs ≤ 25)	2.829 (1.813–4.415)	**< 0.0001**	2.114 (1.589–2.812)	**< 0.0001**
FIGO stage (IV vs III)	9.642 (5.963–15.592)	**< 0.0001**	6.953 (4.744–10.190)	**< 0.0001**
Secondary debulking surgery	< 0.0001 (< 0.0001- > $1.0x10^3$)	0.930	1.277 (0.875–1.862)	0.205

OS overall survival, *PFS* progression-free survival, *HR* hazard ratio, *95% CI* 95% confidence interval, *I3C* indole-3-carbinol, *EGCG* epigallocatechin-3-gallate, *PCI* peritoneal cancer index, *FIGO* International Federation of Gynecology and Obstetrics
NOTE. Bold font indicates $p < 0.05$

vivo, and clinically in OC patients' primary tumors, ascites and secondary tumor foci [19, 20]. In response to adjuvant chemotherapy with platinum derivatives (in combination with taxanes as well as individually), which effectively eliminated the bulk of ovarian tumor cells, those stem cell phenotype cancer cells not only survived but more than that, proliferated and demonstrated elevated tumorigenic and metastatic activity in vivo [44], even after a short–term single treatment of conventional chemotherapy [48].

It was also established that in all patients who suffered from recurrent and metastatic OC after conventional treatment, the rate of CSCs in recurrent tumors and ascites was dramatically higher than in their primary tumors, therefore, ovarian CSCs can be considered a prognostic factor for OC relapse [22]. There is evidence on CSC rate correlating with recurrence and survival of patients with early OC [21]. It was shown that OC-associated ascites acts as a great pool of CSCs whose number and tumorigenic activity dramatically increased after standard chemotherapy [49].

Recently, an independent concept of ovarian CSCs was formulated as part of the overall CSC framework, with a novel ovarian carcinogenesis model leading to a new OC treatment approach based on a combination of conventional chemotherapy drugs with specific ovarian CSC inhibitors [44]. The newly suggested more effective approach to OC management by drug therapy was to target CSCs using specific CSCs inhibitors and kill bulk tumor cells using standard chemotherapy together. There is every reason to believe that the better we understand the regulation of ovarian CSCs activity, the

Table 4 ECOG performance status of patients after combined treatment and at the end of the study

Characteristic	Arm 1 (*n* = 46)	Arm 2 (*n* = 76)	Arm 3 (*n* = 42)	Arms 2+3 (*n* = 118)	Arm 4 (*n* = 40)	Arm 5 (*n* = 80)
ECOG performance status after combined treatment, No. (%)						
0	35 (76.1)	60 (78.9)	32 (76.2)	92 (77.97)	25 (62.5)	49 (61.25)
1	7 (15.2)	10 (13.2)	6 (14.3)	16 (13.56)	8 (20.0)	15 (18.75)
2	3 (6.5)	4 (5.3)	3 (7.1)	7 (5.93)	4 (10.0)	9 (11.25)
3	1 (2.2)	2 (2.6)	1 (2.4)	3 (2.54)	3 (7.5)	7 (8.75)
*p**	0.12	0.0406	0.14	0.0312	0.86	
Alive patients at database cutoff	46 (100)	76 (100)	42 (100)	118 (100)	40 (100)	80 (100)
ECOG performance status at the end of the study, No. (%)						
0	8 (17.4)	15 (19.7)	8 (19.1)	23 (19.49)	2 (5.0)	3 (3.75)
1	9 (19.5)	17 (22.4)	11 (26.2)	28 (23.73)	4 (10.0)	7 (8.75)
2	8 (17.4)	10 (13.2)	7 (16.6)	17 (14.41)	3 (7.5)	6 (7.50)
3	4 (8.7)	4 (5.3)	3 (7.1)	7 (5.93)	4 (10.0)	7 (8.75)
4	1 (2.2)	2 (2.6)	1 (2.4)	3 (2.54)	3 (7.5)	6 (7.50)
*p**	0.0180	0.0013	0.0078	0.0007	0.86	
Death	16 (34.8)	28 (36.8)	12 (28.6)	40 (33.90)	24 (60.0)	51 (63.75)
Alive patients at database cutoff	30 (62.5)	48 (63.2)	30 (71.4)	78 (66.10)	16 (40.0)	29 (36.25)

ECOG Eastern Cooperative Oncology Group
*Mann-Whitney U-test was applied to determine the differences between arms 1–4 vs arm 5 and arms 2+3 vs arm 5

Table 5 Global health status in maintenance therapy arms 1–3, and arms 2+3 versus control arm 5

Characteristic	Arm 1 ($n = 46$)	Arm 2 ($n = 76$)	Arm 3 ($n = 42$)	Arms 2+3 ($n = 118$)	Arm 5 ($n = 80$)
At screening					
MS ± SD	77.51 ± 10.24	78.83 ± 10.35	76.97 ± 10.96	78.18 ± 10.56	78.24 ± 9.75
p*	0.6733	0.7162	0.5236	0.9690	
After combined treatment					
MS ± SD	63.51 ± 9.64	64.95 ± 8.65	63.52 ± 9.77	64.45 ± 9.04	63.98 ± 7.46
p*	0.7475	0.4603	0.7724	0.7085	
At the end of the study					
MS ± SD	55.37 ± 20.48	63.69 ± 14.88	58.23 ± 18.33	61.57 ± 16.41	53.19 ± 16.52
p*	0.6532	**0.0060**	0.2796	**0.0240**	

MS mean score, *SD* standard deviation
*Student's test was applied to determine the differences between arms 1–3 vs arm 5 and arms 2+3 vs arm 5
NOTE. Bold font indicates $p < 0.05$

easier it will be to develop improved therapeutic strategies for recurrent ovarian cancer [50].

To date, multiple anticarcinogenic activities of unique non-toxic natural compounds I3C, its in vivo metabolite 3,3′-diindolylmethane (DIM) (it is considered that all the basic antitumor properties of I3C are due to those of DIM), and EGCG were comprehensively studied in different malignancies and amply described [51–54], including in OC [55–57].

These natural agents have been shown to suppress proliferation of tumor cells, selectively induce their cell cycle arrest and apoptosis. They have also demonstrated anti-angiogenic, anti-migratory, anti-metastatic, anti-inflammatory, and anti-oxidant activity, including at the transcription level. I3C and DIM as ligands of aryl hydrocarbon receptors influence phase-I and II carcinogen and xenobiotic metabolism and normalize abnormal estrogen metabolism by increasing the production of less estrogenic 2-hydroxyestrone and thus improving the 2-hydroxyestrone/16α-hydroxyestrone ratio in blood and estrogen dependent tissues. I3C, DIM, and EGCG also have epigenetic antitumor activity inhibiting the key epigenetic enzymes like DNA methyltransferase [58–61] and histone deacetylase [62–64]. Today EGCG is considered to be one of the most promising anti-cancer agents with DNA-demethylating epigenetic activity comparable to current FDA-approved DNA-demethylating epigenetic drugs [65]. I3C, DIM, and EGCG can also modulate non-coding miRNA expression profiles, leading to the inhibition of cancer cell growth, induction of apoptosis, reversal of epithelial-mesenchymal transition, or enhancement of efficacy of conventional cancer therapeutics [66].

It is very important that I3C [67], DIM [68–70], and EGCG [71–74] were found to be capable of selectively inhibiting CSCs by specifically blocking the key molecular targets responsible for their stemness and chemoresistance, and soluble factors of their proinflammatory niche, determining CSCs tumorigenicity. These targets are: the components of Wnt, Hedgehog, and SHh signaling

Table 6 Functional scales in maintenance therapy arms 1–3, and arms 2+3 versus control arm 5

Characteristic	Arm 1 ($n = 46$)	Arm 2 ($n = 76$)	Arm 3 ($n = 42$)	Arms 2+3 ($n = 118$)	Arm 5 ($n = 80$)
At screening					
MS ± SD	81.23 ± 4.42	82.05 ± 4.62	82.18 ± 4.62	82.09 ± 4.60	81.87 ± 5.16
p*	0.4464	0.8218	0.7500	0.7516	
After combined treatment					
MS ± SD	66.49 ± 5.10	67.51 ± 4.78	66.95 ± 4.84	67.32 ± 4.79	67.15 ± 4.92
p*	0.4440	0.6504	0.8337	0.8202	
At the end of the study					
MS ± SD	50.90 ± 9.74	55.04 ± 6.68	53.41 ± 7.39	54.41 ± 6.96	48.10 ± 6.09
p*	0.2122	**< 0.0001**	**0.0055**	**0.0001**	

MS mean score, *SD* standard deviation
*Student's test was applied to determine the differences between arms 1–3 vs arm 5 and arms 2+3 vs arm 5
NOTE. Bold font indicates $p < 0.05$

Table 7 Symptom scales in maintenance therapy arms 1–3, and arms 2+3 versus control arm 5

Characteristic	Arm 1 ($n = 46$)	Arm 2 ($n = 76$)	Arm 3 ($n = 42$)	Arms 2 + 3 ($n = 118$)	Arm 5 ($n = 80$)
At screening					
MS ± SD	19.68 ± 8.52	19.19 ± 8.90	18.19 ± 7.74	18.84 ± 8.49	19.71 ± 8.94
p*	0.9868	0.7207	0.3619	0.4953	
After combined treatment					
MS ± SD	31.39 ± 8.20	31.25 ± 7.77	31.66 ± 5.57	31.39 ± 7.05	31.25 ± 6.58
p*	0.9135	0.9999	0.7376	0.8870	
At the end of the study					
MS ± SD	34.59 ± 21.53	29.28 ± 20.33	30.01 ± 23.19	29.57 ± 21.34	34.83 ± 19.21
p*	0.9644	0.2494	0.3970	0.2588	

MS mean score, *SD* standard deviation
*Student's test was applied to determine the differences between arms 1–3 vs arm 5 and arms 2+3 vs arm 5

pathways; Nanog, Lin28B, c-Myc, Oct-4, NF-κB, and STAT3 transcription factors; TGFβ, EGF, bFGF growth factors and their receptors, inducible nitric oxide synthase, pro-inflammatory cytokines, matrix metalloproteinases, pro-angiogenic factors VEGF and HIFα, TLR4 receptors, etc. It was also estimated that I3C, DIM and EGCG inhibit epithelial-mesenchymal transition (EMT) signatures, which correlates with essentially reduced CSC's migration and invasion, and subsequent metastasis [75, 76]. It is known that the EMT in cancer cells is associated with CSC's phenotype and their invasive and metastatic activity as well as multidrug resistance.

So there is a broad discussion of possibilities related to using these compounds not only as promising chemopreventive agents, but also as effective adjuvants in combined cancer therapy, enhancing the effect of conventional cancer therapies through additive, synergistic effects and amelioration of deleterious side effects, preventing tumor recurrences, and reducing metastasis. In OC, the capacity of EGCG to enhance cisplatin sensitivity was established [77]. I3C, DIM and EGCG were evaluated in many human phase I and phase II clinical trials as potential chemopreventive agents or chemo-radio-sensitizers in human cancers.

In our trial, oral administration of I3C and EGCG as maintenance therapeutic agents in advanced OC has demonstrated dramatic increase in median OS (almost one and a half times) and median PFS (approximately double). HR levels calculated with multivariate Cox regression analysis indicate that long-term maintenance therapy with I3C as well as maintenance therapy with I3C and EGCG are independent favorable prognostic factors statistically significantly associated with increase in OS and PFS after adjustment for some variables, including PCI, having well-known prognostic value in primary advanced OC [25, 29].

Patients receiving I3C or I3C and EGCG also demonstrated statistically significant dramatic decrease in OC relapses with ascites: 8–9% vs 60–63%. Ascites in OC patients is known to correlate with peritoneal dissemination of OC and unfavorable prognosis [78, 79].

Recent recognition of a fundamental CSCs role in recurrent OC development and the discovery of metastatically active chemoresistant CSCs in ascites has provided additional support, suggesting that ascites facilitates extensive CSCs peritoneal dissemination and emergence of local recurrences and metastatic foci that are resistant to conventional chemotherapy. The hypothesis therefore is that I3C and EGCG, administered as part of maintenance therapy during and after combined treatment, inhibit ovarian CSCs and thereby dramatically decrease ascites relapse incidence, which in turn results in significantly better survival rates and higher median OS and PFS.

Importantly, the benefit of maintenance therapy with I3C as well as I3C and EGCG was first revealed as early as at the presurgery stage. The vast majority of patients (81–85%) in maintenance therapy arms 1–3 could be subjected to successful complete cytoreductive surgery, in which all visible tumor foci were removed. At the same time there was no technical possibility to do so in most patients from control arms 4 and 5. Thus, the vast majority of patients in control arms 4 and 5 could not be subjected to complete cytoreduction, they were optimally debulked to ≤ 1 cm and suboptimally debulked to > 1 cm. The prognostic significance of residual tumor after primary OC surgery has been recognized worldwide, and several scores were developed with a view to better predict it [34, 80]. We have a good reason to believe that the possibility of more radical surgery in most patients from arms 1–3 can be explained by favorable multiple antitumor effect of I3C and EGCG including their anti-CSCs activity established earlier in numerous studies. At presurgery moment, patients from maintenance therapy arms 1–3 had taken I3C and EGCG agents for 14 days prior to NACT, during

Table 8 Treatment-related grade ≥ 2 AEs in ≥ 25% of patients in ≥ 1 treatment arms*

Characteristic	Arm 1 (*n* = 46)	Arm 2 (*n* = 76)	Arm 3 (*n* = 42)	Arm 4 (*n* = 40)	Arm 5 (*n* = 80)
Hematologic, No. (%)					
Anemia (grades 1–2)	35 (76.1)	56 (73.7)	32 (76.2)	31 (77.5)	63 (78.8)
Leukopenia	30 (65.2)	51 (67.1)	28 (66.7)	27 (67.5)	52 (65.0)
Neutropenia	34 (73.9)	54 (71.1)	30 (71.4)	29 (72.5)	59 (73.8)
Trombocytopenia	38 (82.6)	62 (81.6)	35 (83.3)	32 (80.0)	65 (81.3)
Constitutional symptoms, No. (%)					
Fatigue	41 (89.1)	67 (88.2)	37 (88.1)	35 (87.5)	69 (86.3)
Insomnia	40 (87.0)	68 (89.5)	35 (83.3)	34 (85.0)	71 (88.8)
Body weight loss	35 (76.1)	58 (76.3)	32 (76.2)	30 (75.0)	62 (77.5)
Increased perspiration	39 (84.8)	61 (80.3)	34 (81.0)	32 (80.0)	65 (81.3)
Dermatologic, No. (%)					
Alopecia (partial or total)	46 (100)	76 (100)	42 (100)	40 (100)	80 (100)
Nail changes	37 (80.4)	61 (80.3)	34 (81.0)	33 (82.5)	65 (81.3)
Rash	14 (30.4)	23 (30.3)	13 (31.0)	13 (32.5)	27 (33.8)
Gastrointestinal, No. (%)					
Decreased appetite	40 (87.0)	67 (88.2)	37 (88.1)	35 (87.5)	71 (88.8)
Constipation/Diarrhea	12 (26.1)	19 (25.0)	12 (28.6)	11 (27.5)	23 (28.8)
Dispepsia	41 (89.1)	67 (88.2)	38 (90.5)	35 (87.5)	73 (91.3)
Nausea/Vomiting	30 (65.2)	51 (67.1)	27 (64.3)	26 (65.0)	53 (66.3)
Abdominal pain	19 (41.3)	31 (40.8)	18 (42.9)	17 (42.5)	35 (43.8)
Metabolic, No. (%)					
Hypomagnesemia	13 (28.3)	22 (28.9)	13 (31.0)	12 (30.0)	25 (31.3)
Hyper/hyponatremia	14 (30.4)	24 (31.6)	12 (28.6)	13 (32.5)	24 (30.0)
Hypocalcemia	11 (23.9)	17 (22.4)	10 (23.8)	9 (22.5)	20 (25.0)
Alkaline phosphatase increased	12 (26.1)	19 (25.0)	10 (23.8)	10 (25.0)	19 (23.8)
Neuromuscular & skeletal, central nervous system, otic, ocular, No. (%)					
Peripheral neuropathy	10 (21.7)	18 (23.7)	8 (19.0)	10 (25.0)	18 (22.5)
Arthralgia/myalgia	28 (60.9)	45 (59.2)	24 (57.1)	23 (57.5)	49 (61.3)
Dizziness	14 (30.4)	24 (31.6)	13 (31.0)	12 (30.0)	26 (32.5)
Memory impairment	35 (76.1)	58 (76.3)	33 (78.6)	31 (77.5)	60 (75.0)
Ototoxicity	14 (30.4)	24 (31.6)	13 (31.0)	12 (30.0)	25 (31.3)
Retinopathy	11 (23.9)	19 (25.0)	9 (21.4)	9 (22.5)	17 (21.3)
Urogenital, No. (%)					
Pain/difficulty urinating	12 (26.1)	18 (23.7)	11 (26.2)	9 (22.5)	19 (23.8)
Others	14 (30.4)	23 (30.3)	14 (33.3)	13 (32.5)	25 (31.3)

AEs adverse events
*Chi-square criterion was applied to determine the differences between arms
All differences between maintenance therapy arms 1–3 vs control arms 4 and 5 were statistically insignificant ($p > 0.2$)

NACT, and for a time between the last NACT cycle and surgery.

Also, the levels of tumor marker CA-125 were statistically significantly lower in arms 1–3 at presurgery and after combined treatment compared to control (combined treatment alone).

The prolonged administration of I3C and EGCG as maintenance therapeutic agents facilitated a statistically significant improvement in the PS score (Table 4) and key QOL scores as per EORTC QLQ-C 30 (Tables 5 and 6, for references to the prognostic value of QOL and PS see [81–83]).

In addition, I3C and EGCG are safe compounds and have not demonstrated any toxicity. In a previous placebo controlled clinical trial, the level of AEs in the group receiving I3C was not statistically significantly different from that in the placebo group [84].

Our comparative clinical study is the first trial that investigates the efficacy of orally administered I3C and EGCG as long-term maintenance therapeutic agents in advanced ovarian cancer. The results of this study should be regarded as preliminary, and the study itself as hypothesis-generating. More blinded randomized trials on larger samples of OC patients in this treatment regimen are required, with adjustments for as many factors possibly affecting survival and the intrinsic biologic response rate as possible. In addition to PCI, FIGO stage, histological type, and grading, one such factor should be how many NACT cycles the patient needed to achieve an optimal therapeutic efficacy evaluated by CA-125 level dynamics and by tumor response per RECIST at presurgery. In our study, some patients needed only 2 cycles of NACT, while others needed 3 or 4 cycles, and the proportion of "two-cycle" patients was higher in maintenance therapy arms 1–3 (84.8%, 85.5%, 85.7%, respectively) than in control arm 5 (68.8%) (data not shown). Our data nevertheless demonstrated that the suggested and documented maintenance therapy, starting before and continued during the combined treatment and subsequently for 5 years of follow-up, can be considered to be a promising effective and safe approach to increase the efficacy of treatment of advanced ovarian cancer.

Conclusions

In summary, we showed that the usage of suggested doses of I3C and EGCG as pharmaceutical agents prior to and during combined treatment included neoadjuvant platinum-taxane chemotherapy, surgery, and adjuvant platinum-taxane chemotherapy with their subsequent long-term administration can be considered a new promising way of providing maintenance therapy to advanced ovarian cancer patients [85], which achieved much better treatment outcomes, significantly improved patients's survival and quality of life. In the future, these results may contribute to the development of more efficacious and safe treatment approaches and regimens in ovarian cancer and other female reproductive malignancies.

Abbreviations

ACT: Adjuvant chemotherapy; AEs: Adverse events; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CI: Confidence interval; CSCs: Cancer stem cells; CT: Combined treatment; DIM: 3,3′-Diindolylmethane; ECOG: Eastern Cooperative Oncology Group; EGCG: Epigallocatechin-3-gallate; FIGO: International Federation of Gynecology and Obstetrics; HR: Hazard ratio; I3C: Indole-3-carbinol; MRI: Magnetic resonance imaging; NACT: Neoadjuvant chemotherapy; OC: Ovarian cancer; OS: Overall survival; PCI: Peritoneal cancer index; PET-CT: Positron emission tomography-computed tomography; PFS: Progression-free survival; PS: Performance status; QOL: Quality of life; RSCRR: Russian Scientific Center of Roentgenoradiology; EMT: Epithelial-mesenchymal transition

Acknowledgments

We thank Vadim M. Drukh (Peoples' Friendship University of Russia, Moscow, Russian Federation) for the help in performing the statistical analysis and drafting the manuscript and Igor N. Kuznetsov (Ilmixgroup, Joint-Stock Company, Moscow, Russian Federation) for the administrative support during the study. We also thank all the patients for their participation in this study. The authors would also like to thank nurses, physicians, and clinic staff working at the RSCRR for their help and assistance.

Funding

Funding was provided by Federal State Budgetary Institution "Russian Scientific Center of Roentgenoradiology" (RSCRR) of the Ministry of Healthcare of the Russian Federation. The funder had no role in study design, collection, analysis, and interpretation of the data, decision to publish, or in writing the manuscript.

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available because of patient privacy and legal and administrative policies of the medical institution where the study was conducted but are available from the corresponding author on reasonable request and RSCRR Ethics Committee approval.

Authors' contributions

VIK conceived the study and contributed to its conception and design, the analysis and interpretation of data. LAA was the principal investigator of the study and contributed to its organization and coordination, the analysis and interpretation of data and was a Head of the surgical team. ELM contributed to the data analysis and interpretation, wrote the manuscript including final editing. EVG participated in the patient enrollment, collected the patients's clinical data and participated in the interpretation of data. IBA and OIA contributed with the patient enrollment and collected the patients's clinical data and were members of the surgical team. FHS contributed to the conception of the study, the analysis and interpretation of data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The study protocol was approved by the Ethics Committee of the Federal State Budgetary Institution "Russian Scientific Center of Roentgenoradiology" (RSCRR) of the Ministry of Healthcare of the Russian Federation (Moscow), and all study participants submitted written informed consent at the time of enrollment.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

Publisher's Note

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Received: 31 October 2017 Accepted: 3 September 2018
Published online: 20 September 2018

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American Institute of Integrative Oncology
RESEARCH & EDUCATION

CASE STUDY SUBMISSION

Important: In observance of HIPAA and the sacred trust between care giver and patient, absolutely no patient names or identifying information is to be disclosed. Patient privacy is to be preserved. If you attach any medical records, pathology, surgical or laboratory reports, all names are to be removed.

Date	4/29/2019
Clinician Name & Credentials	Shiroko Sokitch MD
Email	drshiroko@hthmc.com

Describe Your Patient (Please SUMMARIZE and use economy of words. You will have 15 minutes to present)

Age, Gender & Ethnicity	37, F, Latina
Body Type	slim
Values *What is most important to this patient? (Quality of Life, Decision Making, Side Effects?)*	Health, children, family, she wants to get well
Stress Resilience	moderate
Other	dad died two months ago of renal cancer that was diagnosed 11/2018, she took care of him, has twin
Primary Diagnosis & Date *(ex. Breast Cancer L, T3 N1 M0, BRCA1 positive, grade 3, Ki67 > 45%)*	CLL, diagnosed 4/15/2019, WBC 23,000
Secondary Diagnosis *(ex. Diabetes Type 2, Obesity)*	Had gastric sleeve done a year before for obesity, lost 70 lbs Had therapeutic abortion 2012, for abnormal fetus, genetic testing on subsequent pregnancies.

Patient Status

☑ New Diagnosis ☐ Recurrence ☐ In Treatment ☐ In Recovery ☐ In Remission ☐ At Risk

Concomitant and/or Complicating Factors *(ex: poorly controlled diabetes, insomnia, poor support system)*	
Adverse Effects of Cancer or Cancer Treatments *(ex. anxiety-depression, diarrhea, peripheral neuropathy)*	not having treatment, is in watch and wait
Relevant Laboratory, Pathology & Medical Reports *(attach a PDF with patient identifying information removed or summarize)*	Varicella zoster 1212 IgG/IgM EBV titers VCA IGg -527, EBNA >600, IgM -0 WBC 23.7 high lymphocytes, reactive lymphocytes, and elevated basophils, 0- eosinophils GGT 8 Thyroid normal

Brief Summary of Recent History

Brief Summary of Additional Relevant Health, Medical, Psycho-Social and/or Family History

Other Relevant Information

Such as Chinese or Ayurvedic diagnosis, Naturopathic/Homeopathic Information, etc. *(ex. Liver Qi Stagnation, Dysbiosis)*

Chinese diagnosis - immune deficiency, kidney qi deficiency,

Brief Summary of Relevant Past Oncology or Medical Treatments

(ex. surgery, radiotherapy, chemotherapy, immunotherapy, hormone therapy, drug therapy)

none see above -watch and wait.

Summary of Recent and Current Treatments

Medical Oncology Care *(surgery, radiotherapy, chemotherapy, immunotherapy, hormone therapy, drug therapy)*

none initiated yet, waiting for test results. Is seeing energy healer, and massage practitioner.

Integrative Oncology Care *(nutraceutical, botanical, phytochemical, acupuncture, energy medicine, other)*

Your 2 Core Questions (stated clearly and succinctly)

1. What is the best treatment for her EBV, shingles virus.
2. What treatment will prevent CLL expansion.

Attached Medical Records for Reference (with patient identifying information removed)

PROPOSED TREATMENT PLAN **Your case will not be reviewed without a completed proposed treatment plan**

Nutriceutical, Phytochemical and Botanical Supplements (name of supplement, dosing)

Foundation Nutrition Supplements:

Targeted Supplements:

Waiting for lab results.

Functional Foods and/or Therapeutic Shake

waiting for lab results

Dietary Guidelines

mitochondrial diet, with high vegetables.
no sugar,
low carbs.

Lifestyle Guidelines

meditation daily
self care
moving back to be closer to family in Florida

Recommended Diagnostics

Referrals to specialists

has an hematologist

Other Notes (please do not include additional notes in your email – notate them here within the case study)

Case Study: Dr. Shiroko Sokitch, MD

RESOURCES
- AIIORE LIBRARY: REFERENCE for CLL
- CHRONIC LYMPHOCYTIC LEUKEMIA: Expert Guidance for Treatment Selection www.clinicaloptions.com/CLLtool
- CANCER.ORG www.cancer.org/cancer/chronic-lymphocytic-leukemia/

PATIENT MB 37 yo Latina F recently diagnosed with CLL (Chronic Lymphocytic Leukemia)
Hematology-Oncology Plan:Wait and Watch

Lab Data Presented
WBC 23,700
Varicella zoster 1212 IgG/IgM
EBV titers VCA IGg -527, EBNA >600, IgM -0
high lymphocytes, reactive lymphocytes, and elevated basophils, 0- eosinophils
GGT 8
Thyroid normal

Lab information provided is not complete No report submitted
We need to see Bone Marrow Biopsy Pathology Report
With receptors and gene expression

Biomarkers:Monitor long term
CBC and diff
Leukocytes
Absolute Lymphocyte Count
Absolute Neutrophil Count
Watch for decrease in Hgb Hct and Platelets
LDH increase
Kidney fx
Liver fx
Serum Vitamin A
Serum Zinc
Viral Titres
Inflammation markers. Hs CRP, IL-6

As dx progresses
- Fatigue/Weakness
- Fever/Chills/Night Sweats
- lymphadenopathy
- splenomegaly
- abnormal CBC + Diff

Some leukemias are linked to viral infections

Sample Support Plan

Foundation Supplements

DFH Mitochondrial NRG 2/2x/day
DFH Vitamin D Supreme 1 bid Vitamin D 10,000 iu daily
DFH Stellar C 1 bid
DFH Buffered Magnesium Chelate 2 bid
DFH Osteoforce 2 bid
DFH Ferrochel 1 q d
DFH Omegavail TG 1000 2 bid
Klaire Therbiotic Complete 1 bid
DFH Prebiomed XOS 1 bid

Targeted Supplements
DFH Zinc Supreme 1 bid
Vitamin A 25,000iu weekly
DFH Annatto E 300mg delta fraction tocotrienols 1 bid
DFH Curcumevail 2 bid
DFH EGCG 2 bid
DFH Grape Seed Extract 1 bid
Health Concerns Enhance Formula 5 pills bid. ** formula below
Clinical Synergy Pure Honokiol 1 bid and 2 at bedtime
Liposomal Glutathione 5 ml bid

<u>BEDTIME</u>
CS Pure Honokiol 2 caps
Melatonin 10-20mg

Support Inflammation Control. (NFkB, TNFa, inflammatory cytokines)
Quench Oxidative Stress
Support Immune Function
Promote apoptosis

TCM
Support Kidney Qi
Nourish yin
Move Stagnant Phlegm
Move Stasis in Middle Jiao

Custom Botanical Formula

Citrus and Pinellia formula
Scutellaria baicalensis
Scutellaria Barbata
Oldenlandia Heydotis
Salvia Milirorrhiza
Astragalus membranaceus
Ganoderma lucidum
Cortex Magnolia
Cornus off.
Rehmannia Glut (cooked

2 teaspoons daily

Isatis tinctoria
Andrographis paniculata
Tanacetum parthenium
Fritillaria thunbergii
Paeonia alba
Schizandra
Lonicera
Tangerine Peel Chen Pi
Glycyrrhiza glabra

Health Concerns Enhance

Isatis extract (Ban Lan Gen and Da Qing Ye)
Milletia extract (Ji Xue Teng)
Astragalus (Huang Qi)
Tremella (Bai Mu Er)
Andrographis (Chuan Xin Lian)
Lonicera (Jin Yin Hua)
Aquilaria (Chen Xiang),
Epimedium (Yin Yang Huo)
Oldenlandia (Bai Hua She She Cao)
Cistanche (Rou Cong Rong)
Lycium fruit (Gou Qi Zi)
Laminaria (Kun Bu)
Tang-kuei (Dang Gui)
Hu-chang (Hu Chang)
American Ginseng (Xi Yang Shen)
Schizandra (Wu Wei Zi)
Ligustrum (Nu Zhen Zi)
Atractylodes (Bai Zhu)
Rehmannia (Shu Di Huang)
Salvia (Dan Shen)
Curcuma (Yu Jin)
Viola (Zi Hua Di Ding)
Citrus (Chen Pi)
Peony (Bai Shao)
Ho Show Wu (He Shou Wu)
Eucommia (Du Zhong)
Cardamon (Sha Ren)
Licorice (Gan Cao)

Suppressing EBV reactivation

- Monolaurin: 1800 mg twice daily
- Olive Leaf: 1000-1500 mg twice daily
- Cat's Claw tincture: 30-60 drops twice daily
- Vitamin A 25,000 per week
- Vitamin C 500mg four times daily
- Zinc picolinate 30 mg twice daily
- Coriolus versicolor 1000-1500mg twice daily
- Astragalus Root 1000-1500mg twice daily

The Effectiveness of Traditional Chinese Medicine in Treating Patients with Leukemia

Yu-Jun Wang, et al

Evidence-Based Complementary and Alternative Medicine Volume 2016, Article ID 8394850, 12 pages http://dx.doi.org/10.1155/2016/839485

Herbs commonly Prescribed in Taiwan in conjunction with standard of care therapy

Whole Herbs	Herb Formulas
Radix Astragali membranaceus	**Gui Pi Tang**
Radix et Rhizoma Salviae miltiorrhizae	Liu Wei Di Huang Wan
Fructus Ligustri Lucidi	Zuo Gui Wan
Sargentodoxa Cuneata	Gui Lu Er Xian Jiao
Herba Hedyotis diffusa	Sheng Mai San
Rhizoma Dioscoreae polystachya	**JiaWei Xiao Yao San**
Bulbus Fritillaria thunbergii	Xue Fu Zhu Yu Tang
Cortex Lycii Radicis	**Xiang Sha Liu Jun Zi Tang**
Radix Glycyrrhizae uralensis	Xin Yi Qing Fei Tang
Semen Ziziphi Spinosae	**Ren Shen Yang Rong Tang**

Integration of Chinese Herbal Medicine Therapy Improves Survival of Patients With Chronic Lymphocytic Leukemia
A Nationwide Population-Based Cohort Study

Tom Fleischer, MS, Tung-Ti Chang, MD, et al Medicine Volume 95, Number 21, May 2016
www.md-journal.com

Single-herb products

Pin yin nomenclature Scientific name

Bai Hua She She Cao	**Hedyotis diffusa**
Yan Hu Suo	Corydalis yanhusuo
Bei Mu	**Fritillaria thunbergii**
Huang Qin	**Scutellaria baicalensis**
Dan Shen	**Salvia miltiorrhiza**
Ban Lan Gen	**Isatis tinctoria**
Ge Gen	Pueraria lobata
Ban Zhi Lian	**Scutellaria barbata**
Ju Hua	Chrysanthemum morifolium
Huang Qi	**Astragalus membranaceus**

Multiherb products
Pin yin nomenclature Scientific name

Zhi Bo Di Huang Wan –
Ma Zi Ren Wan –
Shen Ling Bai Zhu San –
Bu Zhong Yi Qi Tang –
San Zhong Kui Jian Tang –
Zhi Gan Cao Tang –
Ping Wei San –
Gui Pi Tang –
Jia Wei Xiao Yao San –
Du Huo Ji Sheng Tang

CORE NUTRACEUTICALS AND PHYTOCHEMICALS

Green tea and epigallocatechin gallate: In two studies involving adults with leukemia, green tea consumption was associated with a 50% decreased risk of leukemia. The risk was reduced as the number of cups of tea consumed per day and number of years of tea consumption increased.

Curcumin: Curcumin has been shown to inhibit metastasis, invasion, and angiogenesis in animal models and to induce cell death in leukemia cell lines.

Omega-3 fatty acids: Eicosapentaenoic acid (EPA), an omega-3 fatty acid found in sh and sh oil, has been associated with better weight maintenance and response to therapy, fewer complications, and improved survival in cancer patients.

Vitamin D: Vitamin D helps promote healthy cellular differentiation, and several lines of data highlight vitamin D's potential as a preventive and therapeutic agent in a variety of cancers, including leukemia.

Melatonin: Melatonin has demonstrated anti-aging, immunomodulatory, and anticancer properties. Several epidemiologic studies suggest high levels of melatonin may help prevent cancer, possibly by activating the tumor-suppressor molecule p53.

From cancer.org

PATIENT AND CARE PROVIDER INFORMATION

CHRONIC LYMPHOCYTIC LEUKEMIA: Expert Guidance for Treatment Selection
www.clinicaloptions.com/CLLtool

https://www.cancer.org/cancer/chronic-lymphocytic-leukemia/detection-diagnosis-staging/signs-symptoms.html

Signs and Symptoms of Chronic Lymphocytic Leukemia

Many people with chronic lymphocytic leukemia (CLL) do not have any symptoms when it is diagnosed. The leukemia is often found when their doctor orders blood tests for some unrelated health problem or during a routine check-up and they are found to have a high number of lymphocytes.

Even when people with CLL have symptoms, they're often vague and can be symptoms of other things. Symptoms can include the following:

- Weakness
- Fatigue
- Weight loss
- Chills
- Fever
- Night sweats
- Lymphadenopathy
- Splenomegaly: Pain or a sense of "fullness" in the belly (this can make someone feel full after only a small meal), which is caused by an enlarged spleen and/or liver

Many of the signs and symptoms of advanced CLL occur because the leukemia cells replace the bone marrow's normal blood-making cells. As a result, people don't have enough red blood cells, properly functioning white blood cells, and blood platelets.

- **Anemia** is a shortage of red blood cells. It can cause tiredness, weakness, and shortness of breath.
- **A shortage of normal white blood cells (leukopenia) increases the risk of infections.** You might hear the term **neutropenia**, which refers to low levels of neutrophils (a type of granulocyte needed to fight bacterial infections). People with CLL may have very high white blood cell counts

because of excess numbers of lymphocytes (**lymphocytosis**), but the leukemia cells don't fight infection the way normal white blood cells do.

- **A shortage of blood platelets (thrombocytopenia) can lead to excess bruising, bleeding, frequent or severe nosebleeds, and bleeding gums.**

People with CLL have a higher risk of infections. This is mainly because their immune systems aren't working as well as they should. CLL is a cancer of B lymphocytes, which normally make antibodies that help fight infection. Because of the CLL, these antibody-making cells don't work as they should, so they can't fight infections. Infections may range from simple things like frequent colds or cold sores to pneumonia and other serious infections.

CLL can also affect the immune system in other ways. In some people with CLL, the immune system cells make abnormal antibodies that attack normal blood cells. This is known as **autoimmunity**. It can lead to low blood counts. If the antibodies attack red blood cells, it's called **autoimmune hemolytic anemia**. Less often, the antibodies attack platelets and the cells that make them, leading to low platelet counts. Rarely, the antibodies attack white blood cells, leading to leukopenia (low white blood cell counts).

These symptoms and signs may be caused by CLL, but they can also be caused by other conditions. Still, if you have any of these problems, it's important to see a doctor right away so the cause can be found and treated, if needed

https://www.cancer.org/cancer/chronic-lymphocytic-leukemia/treating/treatment-by-risk-group.html

Typical Treatment of Chronic Lymphocytic Leukemia

CLL mainly affects older adults. The average age at the time of diagnosis is around 70years. It's rarely seen in people under age 40, and is extremely rare in children.

Treatment options for chronic lymphocytic leukemia (CLL) vary greatly, depending on the person's age, the disease risk group, and the reason for treating (for example, which symptoms it is causing). Many people live a long time with CLL, but in general it is very difficult to cure, and early treatment hasn't been shown to help people live longer. Because of this and because treatment can cause side effects, doctors often advise waiting until the disease is progressing or bothersome symptoms appear, before starting treatment.

If treatment is needed, factors that should be taken into account include the patient's age, general health, and prognostic factors such as the presence of deletions in chromosomes 17 or 11, or high levels of ZAP-70 and CD38.

Initial treatment of CLL

Drugs that may be used

Patients who might not be able to tolerate the side effects of strong chemotherapy (chemo) are often treated with chlorambucil with a monoclonal antibody like obinutuzumab (Gazyva). Other options include the targeted drug ibrutinib (Imbruvica) alone, and rituximab alone or with a corticosteroid like prednisone.

There are other options, too.

In stronger and healthier patients, commonly used treatments include:

- FCR: fludarabine (Fludara), cyclophosphamide (Cytoxan), and rituximab
- Bendamustine (sometimes with a CD20 monoclonal antibody)
- Ibrutinib (alone or with obinutuzumab)
- FR: fludarabine and rituximab
- High-dose prednisone and rituximab
- PCR: pentostatin (Nipent), cyclophosphamide, and rituximab
- Alemtuzumab (Campath) with rituximab

Other drugs or combinations of drugs may also be used.

Radiation or surgery

If the only problem is an enlarged spleen or swollen lymph nodes in one part of the body, localized treatment with low-dose radiation therapy may be used. Splenectomy (surgery to remove the spleen) is another option if the enlarged spleen is causing symptoms.

Leukapheresis

Sometimes very high numbers of CLL cells in the blood cause problems with normal circulation. This is called **leukostasis**. Chemo may not lower the number of cells until a few days after the first dose, so before the chemo is given, some of the cells may need to be removed from the blood with a procedure called **leukapheresis**. This treatment lowers blood counts right away. The effect lasts only for a short time, but it may help until the chemo has a chance to work. Leukapheresis is also sometimes used before chemo if there are very high numbers of leukemia cells (even when they aren't causing problems) to prevent tumor lysis syndrome. (This was discussed in the chemotherapy section.)

Stem cell transplant

Some people who have very high-risk disease (based on prognostic factors) may be referred for possible stem cell transplant (SCT) early in treatment.

Second-line treatment of CLL

If the initial treatment is no longer working or the disease comes back, another type of treatment often helps. If the initial response to the treatment lasted a long time (usually at least a few years), the same treatment might be used again. If the initial response wasn't long-lasting, using the same treatment isn't as likely to be helpful. The options will depend on what the first-line treatment was and how well it worked, as well as the person's overall health.

Many of the drugs and combinations listed above may be options as second-line treatments, too. Targeted therapy and monoclonal antibody drugs are commonly used, alone or in combination. Other chemo drugs may also be tried.

If the leukemia responds, stem cell transplant may be an option for some patients.

Some people may have a good response to first-line treatment (such as fludarabine) but may still have some evidence of a small number of leukemia cells in the blood, bone marrow, or lymph nodes. This is known as **minimal residual disease.** CLL can't be cured, so doctors aren't sure if further treatment right away will be helpful. Some small studies have shown that alemtuzumab can sometimes help get rid of these remaining cells, but it's not yet clear if this improves survival.

Treating complications of CLL : One of the most serious complications of CLL is a change (transformation) of the leukemia to a high-grade or aggressive type of non-Hodgkin lymphoma (NHL) called diffuse large B-cell lymphoma (DLBCL) or to Hodgkin lymphoma. This happens in 2% to 10% of CLL cases, and is known as Richter's transformation. Treatment is often the same as it would be for lymphoma and might include stem cell transplant, because these cases are often hard to treat.

Less often, CLL may progress to prolymphocytic leukemia. As with Richter syndrome, this, too, can be hard to treat. Some studies have suggested that certain drugs such as cladribine (2-CdA) and alemtuzumab may be helpful.

In rare patients with CLL, the leukemia transforms into acute lymphocytic leukemia (ALL). If this happens, treatment is likely to be similar to that used for patients with ALL.

Acute myeloid leukemia (AML) is another rare complication in patients who have been treated for CLL. Drugs such as chlorambucil and cyclophosphamide can damage the DNA of blood-forming cells. These damaged cells may go on to become cancer, leading to AML, which is very aggressive and often hard to treat.

CLL can cause problems with low blood counts and infections.

Newer Therapies: Vaccines, CAR-T cell therapy

Supportive Care for Chronic Lymphocytic Leukemia

https://www.cancer.org/cancer/chronic-lymphocytic-leukemia/treating/supportive-care.html

Supportive care for chronic lymphocytic leukemia (CLL) is aimed at helping with problems related to the cancer and its treatment. It's not treatment for the CLL itself. For instance, some people with CLL have problems with infections or low blood counts. Although treating the CLL may help these over time, other treatments may be needed in the meantime.

Treatments to prevent infections

Intravenous immunoglobulin (IVIG)

Some people with CLL don't have enough antibodies (immunoglobulins) to fight infection. This can lead to repeated lung and/or sinus infections. Antibody levels can be checked with a blood test, and if they're low, antibodies from donors can be given into a vein (IV) to raise the levels and help prevent infections. These donated antibodies are called intravenous immunoglobulin or IVIG. IVIG is often given once a month at first, but can also be given as needed based on blood tests of antibody levels.

Antibiotics and anti-virals

Certain chemo drugs (such as purine analogs – see the chemotherapy section for details) and the antibody drug alemtuzumab (Campath) can raise your risk of certain infections such as CMV (a virus) and pneumonia caused by *Pneumocystis jiroveci*. You might be given an anti-viral drug like acyclovir or valacyclovir (Valtrex®) to help lower the risk of CMV infections. To help prevent Pneumocystis pneumonia, a sulfa antibiotic is often given (trimethoprim with sulfamethoxazole, which is often known by the brand names Septra® or Bactrim®). Other treatments are available for people who are allergic to sulfa drugs.

Some drugs used to treat CLL can also cause dormant viruses to become active. For instance, if you already carry the hepatitis virus or CMV, treatment may allow them to grow and cause problems. Blood tests will be done to watch virus levels. Drugs may be used to help keep these viruses under control.

Using drugs to help prevent infections this way may be called anti-infective prophylaxis. Antibiotics and anti-viral drugs are also used to treat infections. Often, active infections require higher doses or different drugs than are used to prevent infections.

Routine Vaccines (opinion of conventional oncology hematologyy)

It's best for people with CLL to speak to their health care provider before getting any vaccine.

Experts recommend that people with CLL get the pneumonia vaccine every 5 years. They also recommend a yearly flu shot (influenza vaccine).

Avoid vaccines that contain live viruses.

For more information on vaccines, see Vaccination During Cancer Treatment.

Treatments for low blood counts

CLL or its treatment can cause low blood cell counts . Low red blood counts cause anemia. Anemia can make you feel tired, light headed, or short of breath from walking. If anemia is causing symptoms, it can be treated with transfusions. These are often given in an outpatient clinic. If platelet counts get very low, it can lead to serious bleeding. Platelet transfusions can help prevent this.

In CLL, low red blood and platelet counts can also be caused by the cells being destroyed by abnormal antibodies. When antibodies cause low numbers of platelets, it's called **immune thrombocytopenic purpura** or ITP. Before diagnosing this, the doctor often needs to check the bone marrow to make sure that there isn't another cause for the low platelet counts. In ITP, giving platelet transfusions doesn't usually help increase the platelet counts much, if at all, because the antibodies just destroy the new platelets, too. This can be treated by drugs that affect the immune system, like corticosteroids, IVIG, and the antibody drug rituximab (Rituxan®). Another option is to remove the spleen , since after the antibodies stick to the platelets, they're actually destroyed in the spleen. Another option is a drug that tells the body to make more platelets, like eltrombopag (Promactac®) or romiplostim (Nplate®).

When antibodies cause low red blood cell counts, it's called **autoimmune hemolytic anemia** (AIHA). This also can be treated with drugs that affect the immune system, like corticosteroids, IVIG, and rituximab (Rituxan). Removing the spleen is another option. If you develop AIHA while taking fludarabine (Fludara®), the drug may be the cause so it will be stopped.

- References

https://www.cancer.org/cancer/chronic-lymphocytic-leukemia/detection-diagnosis-staging/staging.html

How is Chronic Lymphocytic Leukemia Staged?

For most cancers, staging is the process of finding out how far the cancer has spread. Stages are often useful because they can help guide treatment and determine a person's outlook. Most types of cancer are staged based on the size of the tumor and how far the cancer has spread.
Chronic lymphocytic leukemia (CLL), on the other hand, does not usually form tumors. It's generally in the bone marrow and blood. And, in many cases, it has spread to other organs such as the spleen, liver, and lymph nodes by the time it's found. The outlook for a person with CLL depends on other information, such as the results of lab test and imaging tests.

Staging systems for chronic lymphocytic leukemia

A staging system is a standard way for the cancer care team to describe cancer. There are 2 different systems for staging CLL:

- **Rai system:** This is used more often in the United States.
- **Binet system:** This is used more widely in Europe.
-

Both of these staging systems are helpful and have been in use for many years.

Rai staging system

The Rai system is based on lymphocytosis. The patient must have a high number of lymphocytes in their blood and bone marrow that isn't linked to any other cause (like infection).
For a diagnosis of CLL, the overall lymphocyte count does not have to be high, but the patient must have at least 5,000/mm3 monoclonal lymphocytes (sometimes called a monoclonal lymphocytosis).

Monoclonal means that the cancer cells all came from one original cell. This causes them to have the same chemical pattern which can be seen with special testing.
This system divides CLL into 5 stages based on the results of blood tests and a physical exam:

- **Rai stage 0:** Lymphocytosis; no enlargement of the lymph nodes, spleen, or liver; red blood cell and platelet counts are near normal.
- **Rai stage I:** Lymphocytosis; enlarged lymph nodes; spleen and liver are not enlarged; red blood cell and platelet counts are near normal.
- **Rai stage II:** Lymphocytosis; enlarged spleen (and maybe an enlarged liver); lymph nodes may or may not be enlarged; red blood cell and platelet counts are near normal.
- **Rai stage III:** Lymphocytosis; lymph nodes, spleen, or liver may or may not be enlarged; red blood cell counts are low (anemia); platelet counts are near normal.
- **Rai stage IV:** Lymphocytosis; enlarged lymph nodes, spleen, or liver; red blood cell counts may be low or near normal; platelet counts are low (thrombocytopenia).
-

Doctors separate the Rai stages into low-, intermediate-, and high-risk groups when determining treatment options.

- Stage 0 is low risk.
- Stages I and II are intermediate risk.
- Stages III and IV are high risk.

These risk groups are used later in Treatment of Chronic Lymphocytic Leukemia.

Binet staging system
In the Binet staging system, CLL is classified by the number of affected lymphoid tissue groups (neck lymph nodes, groin lymph nodes, underarm lymph nodes, spleen, and liver) and by whether or not the patient has anemia (too few red blood cells) or thrombocytopenia (too few blood platelets).

- **Binet stage A:** Fewer than 3 areas of lymphoid tissue are enlarged, with no anemia or thrombocytopenia.
- **Binet stage B:** 3 or more areas of lymphoid tissue are enlarged, with no anemia or thrombocytopenia.
- **Binet stage C:** Anemia and/or thrombocytopenia are present. Any number of lymphoid tissue areas may be enlarged.

Prognostic factors for chronic lymphocytic leukemia

Along with the stage, there are other factors that help predict a person's outlook. These factors are not part of formal staging systems (at least at this time), but are often taken into account when looking at possible treatment options.

- Factors that tend to be linked with shorter survival time are called **adverse prognostic factors**.
- Those that predict longer survival are **favorable prognostic factors**.

Adverse prognostic factors

- Diffuse pattern of bone marrow involvement (more widespread replacement of normal marrow by leukemia)
- Advanced age
- Deletions of parts of chromosomes 17 or 11
- Trisomy 12 in the CLL cells
- High blood levels of certain substances, such as beta-2-microglobulin

- Lymphocyte doubling time (the time it takes for the lymphocyte count to double) of less than 1 year
- Increased fraction of prolymphocytes (an early form of the lymphocyte) in the blood
- High proportion of CLL cells containing ZAP-70 (20% or more) or CD38 (30% or more)
- CLL cells with unchanged (not mutated) gene for the immunoglobulin heavy chain variable region (IGHV)
- CLL cells don't have the TP53 gene
-

Favorable prognostic factors

- Non-diffuse (nodular or interstitial) pattern of bone marrow involvement
- Deletion of part of chromosome 13 (with no other chromosome abnormalities)
- Low proportion of CLL cells containing ZAP-70 (less than 20%) or CD38 (less than 30%)
- CLL cells with a mutated gene for IGHV
-

Certain prognostic factors such as the presence or absence of ZAP-70, CD38, and a mutated gene for IGHV help divide cases of CLL into 2 groups, slow growing and fast growing. People with the slower growing kind of CLL tend to live longer and may be able to delay treatment longer as well.

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Integration of Chinese Herbal Medicine Therapy Improves Survival of Patients With Chronic Lymphocytic Leukemia

A Nationwide Population-Based Cohort Study

Tom Fleischer, MS, Tung-Ti Chang, MD, PhD, Jen-Huai Chiang, MS, Ching-Yun Hsieh, MD, Mao-Feng Sun, MD, PhD, and Hung-Rong Yen, MD, PhD

Abstract: Utilization of Chinese Medicine (CM) is not uncommon in patients with chronic lymphocytic leukemia (CLL). However, the current knowledge of the usage and efficacy of CM among CLL patients is limited. The aim of this study was to determine the impact of integrative Chinese Herbal Medicine (CHM) on the disease course of CLL and ascertain the herbal products most commonly prescribed to patients with CLL.

A Taiwanese nationwide population-based study involving the use of Western medicine and CM services provided by the National Health Insurance (NHI) was conducted.

An NHI Research Database-based cohort study was performed; the timeframe of the study was January 2000 to December 2010. The end of the follow-up period was defined as December 31, 2011.

A total of 808 patients were diagnosed with CLL in Taiwan within the defined study period. After randomly matching for age and sex and excluding patients younger than 18 years of age, data from 616 patients were analyzed.

The 2 study groups both received standard of care treatment. In addition, 1 group also received CHM. Patients who were registered as receiving other forms of CM, such as acupuncture, were excluded.

Hazard ratios of mortality were used to determine the influence of CHM and the therapeutic potential of herbal products.

In total, 616 CLL patients were included in the analyses. We found that the HR associated with the adjunctive use of CHM was less than half when compared to the non-CHM group (0.43, 95% CI 0.33–0.55, $P < 0.0001$) and that treatment-naive patients who used CHM had the lowest HR. We also established that this association between reduction in HR and CHM was dose-dependent, and the longer CHM users received prescriptions, the lower the HR ($P < 0.001$).

We supplied data from a relatively large population that spanned a significant amount of time. Our data suggests that the treatment of CLL with adjunctive CHM may have a substantial positive impact on mortality, especially for treatment-naive patients. Further research is needed to confirm whether there is a direct causal relationship between CHM and the outcomes displayed.

(*Medicine* 95(21):e3788)

Abbreviations: CHF = congestive heart failure, CHM = Chinese Herbal Medicine, CKD = chronic kidney disease, CLL = chronic lymphocytic leukemia, CM = Chinese Medicine, COPD = chronic obstructive pulmonary disease, FCR = Fludarabine Cyclophosphamide Rituximab, ICD = International Classification of Diseases Ninth Revision, Clinical Modification, NHI = National Health Insurance, NHIRD = National Health Insurance Research Database.

INTRODUCTION

Chronic lymphocytic leukemia (CLL) is a hematologic malignancy which is characterized by clonal proliferation and accumulation of lymphoid B cells in the blood, bone marrow, lymph nodes, and spleen.[1] The fludarabine cyclophosphamide rituximab (FCR) chemoimmunotherapy regimen has become the standard first-line therapy, after decades of using chemotherapeutic agents alone.[2] Recent years have also been marked by the emergence of agents such as Idelalisib and Ibrutinib, which inhibit BCR signaling, and have shown positive results for both treatment-naive and relapsed CLL patients.[3–6] Venetoclax (ABT-199) and chimeric antigen receptor T cells are examples of therapies that tackle CLL from different approaches, adding to the growing arsenal of options that physicians may choose from.[7,8] With all these new and

Editor: Roman Leischik.
Received: January 11, 2016; revised: April 29, 2016; accepted: May 4, 2016.
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TF and T-TC contributed equally to this study.
Funding: this study was supported by China Medical University under the Aim for Top University Plan of the Ministry of Education, Taiwan. This study was also supported in part by China Medical University Hospital (DMR-105-005) and the Taiwan Ministry of Health and Welfare Clinical Trial and Research Center of Excellence (MOHW105-TDU-B-212-133019). This study was based, in part, on data from the National Health Insurance Research Database, provided by the National Health Insurance Administration, Ministry of Health and Welfare, and managed by National Health Research Institutes. The interpretation and conclusions contained herein do not represent those of the National Health Insurance Administration, Ministry of Health and Welfare, or National Health Research Institutes. The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.
The authors have no conflicts of interest to disclose.

ISSN: 0025-7974
DOI: 10.1097/MD.0000000000003788

emerging drugs in the market, one might wonder whether any available therapies have been overlooked.

There are practically no published data concerning the efficacy of Chinese Medicine (CM) in the treatment of CLL. A case report from 2003 mentioned full remission in 1 patient, following the use of Chinese Herbal Medicine (CHM) alone.[9] Other cell-line and animal model studies have focused mainly on herbs or compounds from within the CHM pharmacopeia, that may be beneficial for CLL patients, for example, Indirubin, Curcumin, *Hedyotis diffusa,* and *Ganoderma lucidum* to name a few.[10–13] Clinical trials of CM in China have been steadily increasing in the past 30 years, and reviews have shown that 11% of these trials are on leukemia.[14] Unfortunately, these trials have not reached the standards required by science citation indexed journals and have thus failed to reach western readership. It is clear that much stronger evidence is needed before establishing any potential role that CM might have in the management of CLL.

CM has been regarded as a kind of complementary therapies in the Western countries. However, it has been one of the mainstream therapies in some Asian countries, such as Taiwan, Korea, and China. [15,16] Approximately 30% of Taiwanese sought CM service covered by the National Health Insurance (NHI) program.[17] This compulsory NHI was launched in 1995 and covered >99% of the Taiwanese population.[18] Ever since 1996, the NHI program has started to reimburse CM service provided by qualified Chinese medical doctors, including acupuncture, moxibustion, Chinese orthopedics and traumatology, and Chinese herbs.

All registration files and original claim data in the NHI program are registered in the Taiwanese NHI Research Database (NHIRD) and managed by National Health Research Institutes in Taiwan. In recent years, this database has played an increasing role in shedding light on the potential of CM on critical illnesses such as diabetes,[19] stroke,[20] and cancer.[21] Because CHM is more commonly provided to patients in Taiwan among the different modalities of treatments, we chose to focus on CHM. Also, 100% of the Chinese herbal products provided in the NHI program are manufactured by Good Manufacturing Practice (GMP)-certified pharmaceutical factories and 80% of them are manufactured by Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S) GMP-certified pharmaceutical factories. These Chinese herbal products are in the form of granules, including single-herb products (single Chinese herbs) or multiherb products (Chinese herbal formulas).[21]

Due to the complete lack of data on this topic, we used the NHIRD to conduct a nationwide population-based retrospective cohort study comparing the outcomes of CHM users and nonusers diagnosed with CLL.

METHODS

Database

As CM is part of the NHI policy in Taiwan, we used the National Health Insurance Research Database (NHIRD), to perform a nationwide population-based cohort study. The NHIRD contains information regarding each clinical visit and hospitalization incident of all its beneficiaries, as well as treatment received, and drugs or CHM prescribed. The NHIRD established a *Registry for Catastrophic Illnesses Patient Database* (RCIPD), including ~30 disease categories such as infantile cerebral palsy, cancer, and rheumatoid arthritis.[22] The description of this database has been reported in our previous publications.[21,22] In brief, CLL patients who received comprehensive clinical and laboratory examinations, followed by regular review by hemato-oncologists commissioned by the National Health Insurance Administration, were granted for catastrophic illness certificates. Patients holding such certificates are free of co-payment. All diseases in the NHIRD are classified using the International Classification of Diseases Ninth Revision, Clinical Modification (ICD-9-CM). For this study, we collected patient information through the RCPID file, which included the entire NHI records of all CLL (ICD-9-CM code: 204.1) patients in Taiwan. We then matched these patients corresponding information, including comorbidities, in the NHIRD inpatient and outpatient files.

Study Population

We included all patients, aged 18 years and above, who were diagnosed with CLL between January 2000 and December 2010 in Taiwan. The end of follow-up period was defined as December 31, 2011. It should be noted that it is impossible to differentiate between CLL and the closely-related condition small lymphocytic lymphoma (SLL) based on ICD-9-CM 204.1 alone, and therefore, there is a high probability that this cohort contains patients with SLL as well. Both groups were age and sex matched. When analyzing the hazard ratio for comorbidities of these patients, the following ICD-9-CM codes were used: hypertension (ICD-9-CM 401–405), diabetes (ICD-9-CM 250), congestive heart failure (CHF, ICD-9-CM 428), stroke (ICD-9-CM 430–438), chronic obstructive pulmonary disease (COPD, ICD-9-CM 490–496), cirrhosis (ICD-9-CM 571), chronic kidney disease (CKD, ICD-9-CM 580–589), and anemia (ICD-9-CM 280–285).

Statistical Analysis

In this study, SAS 9.4 (SAS Institute Inc., Cary, NC) was used for statistical analysis. For categorical variables, chi-square or fisher exact test was used to determine the statistical differences between 2 groups. For continuous variables, the independent *t* test was used. A Cox proportional hazard model, accounting for age, gender, urbanization level, and the comorbidities mentioned in the results, with a 95% confidence interval (CI), was used to estimate the hazard ratios (HR). For categorical covariates, Kaplan–Meier and log rank tests were performed. A P value <0.05 was considered statistically significant.

Ethical Considerations

This study was conducted in accordance with the Helsinki Declaration. All of the datasets from the NHIRD were encrypted and de-identified to protect enrollee privacy. It was not possible to identify individual patients by any means. The Research Ethics Committee of China Medical University and Hospital approved this study (CMUH104-REC2-115).

Availability of Supporting Data

All data in the NHIRD are properly maintained by the National Health Research Institutes in Taiwan (http://nhird.nhri.org.tw/en/index.html) for research purpose only. Researchers who fulfill the requirements of conducting research, approved by an institutional review board and follow the Computer-Processed Personal Data Protection Law (http://www.winklerpartners.com/?p=987) and related regulations of

TABLE 1. Characteristics of Chronic Lymphocytic Leukemia Patients Differentiated According to Utilization of Chinese Medicine

	CHM				
	No (N = 306)		Yes (N = 310)		
	n	%	n	%	*P* Value
Gender*					0.9636
Female	111	36.27	113	36.45	
Male	195	63.73	197	63.55	
Age mean ± SD†(years)	69.64 (12.28)		66.48 (10.76)		0.0007
Age group‡					0.9430
18–39	2	0.65	2	0.65	
40–59	69	22.55	72	23.23	
≥60	235	76.80	236	76.13	
Urbanization level*,§					0.7167
1 (highest)	74	24.18	72	23.23	
2	84	27.45	92	29.68	
3	61	19.93	52	16.77	
4 (lowest)	87	28.43	94	30.22	
Number of comorbidities*					0.5875
<2	101	33.01	96	30.97	
≥2	205	66.99	214	69.03	
Comorbidites					
Hypertension*	190	62.09	165	53.23	0.0260
Diabetes*	88	28.76	93	30.00	0.7351
CHF*	28	9.15	26	8.39	0.7377
Stroke *	61	19.33	59	19.03	0.7774
COPD*	130	42.48	147	47.42	0.2182
Cirrhosis*	79	25.82	118	38.06	0.0011
Anemia*	85	27.78	92	29.68	0.6024
CKD*	56	18.30	62	20.00	0.5920
Treatment*					0.0142
Yes (received drug treatment)	209	68.30	239	77.10	
No (treatment-naive)	97	31.70	71	22.90	
Drug use					
Fludarabine*	36	11.76	41	13.23	0.5835
Rituximab*	26	8.50	27	8.71	0.9249
Cyclophosphamide*	100	32.68	115	37.10	0.2502
Chlorambucil*	169	55.23	196	63.23	0.0434
Baseline CCI score*					0.1140
0	146	47.71	173	55.81	
1	65	21.24	60	19.35	
≥2	95	31.05	77	24.84	
HSCT					
No	0	0	0	0	
Yes	0	0	1	100	
Follow time (mean in years)‖	2.67 (2.39)		4.59 (2.85)		

CHM included only Chinese Herbal Medicine, excluded acupuncture, and manual therapies.

CCI = Charlson Comorbidity Index, CHF = congestive heart failure, CHM = Chinese Herbal Medicine, CM = Chinese medicine, CKD = chronic kidney disorder, COPD = chronic obstructive pulmonary disease, HSCT = hematopoietic stem cell transplantation, HR = hazard ratio, SD = standard deviation.

*Chi-square test.

†*t*-test.

‡Fisher-exact test.

§The urbanization level was categorized by the population density of the residential area into 4 levels, with level 1 as the most urbanized and level 4 as the least urbanized.

‖Cessation of follow time was defined as expiration or end of study timeframe.

National Health Insurance Administration and National Health Research Institutes can apply for the datasets. All applications are reviewed for approval of data release.

RESULTS

Of the total number of patients diagnosed with CLL between 2000 and 2011 who met our criteria, 616 were age- and sex-matched and included into our study, n = 306 in the non-CHM and n = 310 in the CHM group. (Table 1, Figure 1). In accordance with previous studies, the ratio of male to female patients in our cohort was ~2:1.[23] After age matching, the mean age of the non-CM group was 3.16 years greater than that of the CHM group (69.64 ± 12.28 vs 66.48 ± 10.76, respectively). Additionally, the NHIRD categorizes the level of urbanity based on the population density where the event occurred (people/km^2). In this respect, we found that there was no significant difference between both groups. The prevalence of liver cirrhosis and hypertension was higher by 12.24% and lower by 8.86%, respectively, in non-CHM users. The percentage of treatment-naive patients in the non-CHM group was higher by 8.8% than the CHM group ($P = 0.0142$). Furthermore, chlorambucil was found to be prescribed 8% more in the CHM group. No significant differences were found in respect to the Charlson Comorbidity Index (CCI) or number of patients who received hematopoietic stem cell transplantation (HSCT). The mean follow-up time was 2.67 years for non-CHM users and 4.59 years for CM users ($P < 0.0001$).

After inserting age, gender, urbanization level, number of comorbidities, treatments, and drugs used into the regression model, CHM users had a much lower HR of mortality (0.43, 95% CI 0.33–0.55, $P < 0.0001$) compared to non-CHM group users (Table 2). Furthermore, in Table 2 the cohort was subgrouped according to standard of care treatment and it was shown that CHM users experienced a decrease of HR compared to non-CHM users, in both the treatment and treatment-naive subgroups (0.53, 95% CI 0.40–0.71, $P < 0.0001$, and 0.19, 95% CI 0.10–0.38, $P < 0.0001$, respectively). The difference in mortality between the subgroups was also illustrated through a Kaplan–Meier survival graph (Figure 2), which displayed a consistent difference in the mortality rate between the groups, in favor of the CHM users ($P < 0.0001$).

Table 3 reveals the distribution of CHM users according to their accumulated days of herbal prescriptions. Using patients with < 30 days of CHM use (including nonusers, n = 416) as the reference, it was observed that patients who accumulated between 30 and 180 days of herbal prescriptions (n = 141) experienced an HR of 0.57 (95% CI 0.42–0.79, $P < 0.001$). The risk of mortality of CHM users who had accumulated >6 months of herbal prescriptions was lower still (HR 0.35, 95% CI 0.21–0.60, $P < 0.001$).

In Table 4, the HR of the 10 singleherb and multiherb products most commonly prescribed for the treatment of CLL are listed. With exception of 2 herbal products (*Scutellaria barbata*, Ping Wei San), all others were associated with significant reductions in HR.

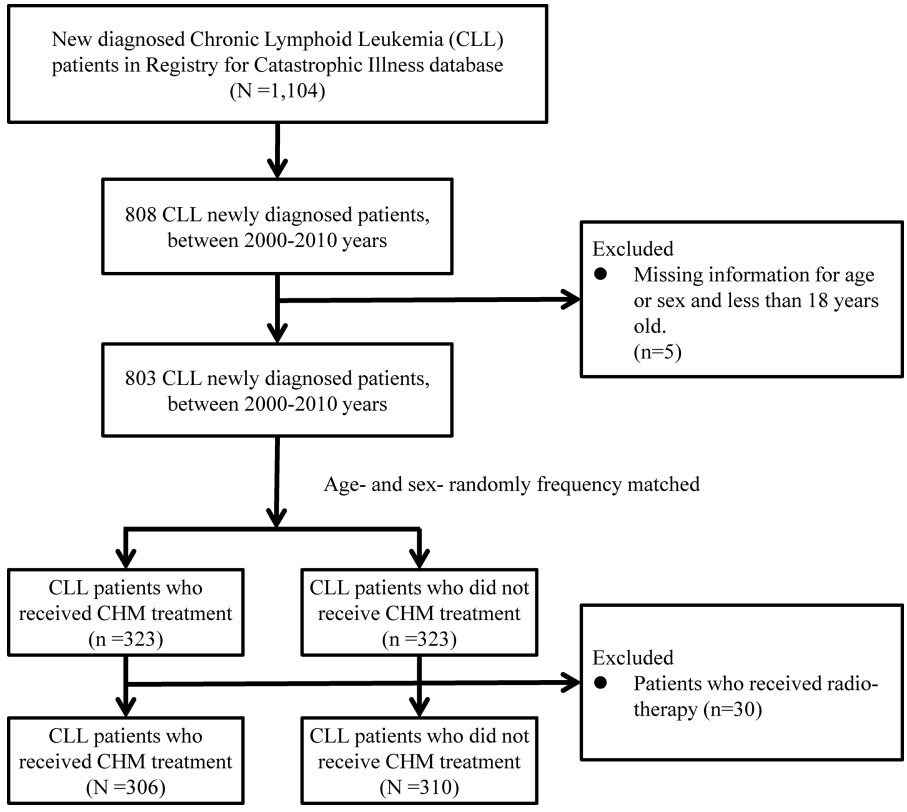

FIGURE 1. Study population flowchart diagram. Of the total number of chronic lymphoid leukemia (CLL) patients registered in the NHIRD (n = 1104), 808 patients were diagnosed within the years 2000 to 2010. After excluding patients with missing information who were aged >18 and after matching 1:1 by age and sex, both groups contained 323 patients. CLL = chronic lymphocytic leukemia, NHIRD = National Health Insurance Research Database.

TABLE 2. Cox Proportional Hazard Regression With Hazard Ratios and 95% Confidence Intervals of Mortality Associated With CHM and Covariates Among Chronic Lymphocytic Leukemia Patients

	Frequency of Mortality	Crude*			Adjusted†		
Variable	**(n = 241)**	**HR**	**(95% CI)**	***P* Value**	**HR**	**(95% CI)**	***P* Value**
CHM							
No	138	1	Reference		1	Reference	
Yes	103	0.44	(0.34–0.57)	<0.0001	0.43	(0.33–0.55)	<0.0001
Received treatment							
Non-CHM	98	1	Reference		1	Reference	
CHM	92	0.52	(0.39–0.70)	<0.0001	0.53	(0.40–0.71)	<0.0001
Treatment-naïve							
Non-CHM	40	1	Reference		1	Reference	
CHM	11	0.2	(0.10–0.40)	<0.0001	0.19	(0.10–0.38)	<0.0001

CHF = congestive heart failure, CHM = Chinese Herbal Medicine, CI = confidence interval, CKD = chronic kidney disorder, COPD = chronic obstructive pulmonary disease, HR = hazard ratio.

*Relative hazard ratio.

†adjusted hazard ratio: mutually adjusted through Cox proportional hazard regression model for CHM use, age group, gender, urbanization level, hypertension, diabetes, congestive heart failure, chronic obstructive pulmonary disease, chronic kidney disorder, number of comorbidities (<2, ≥2), treatment and drugs used including fludarabine, rituximab, cyclophosphamide, and chlorambucil.

DISCUSSION

Our study is the first to comprehensively include leukemia patients from a period of 10 years and illustrate their utilization of Western medicine and CHM in Taiwan. Furthermore, we have found that integrative CHM therapy may be beneficial for patients with CLL. In Italy, it was reported that the rate of CLL patients seeking Complementary and Alternative Medicine (CAM) was 16%;[24] a different study in Germany reported rates of 44%.[25] Additionally, 6.9% of these German patients stated that they had used acupuncture, but the therapy most commonly used in these 2 studies was vitamin supplementation. No thorough data exists regarding the use of CM among patients in western countries, let alone of CLL patients, yet it is clear that the Taiwanese rates of utilization are comparatively high. During our analyses, we discovered that between 2000 and 2011, approximately half of the CLL patients in Taiwan made use of the CM offered in the NHI program. Furthermore, during the exclusion process, we found that 98% of the CM users among CLL patients received CHM and only very few of them received acupuncture treatment alone. This is not surprising when taking into account the fact that CM in Asia emphasizes the use of herbs, and as much as 85% of the CM treatments carried out within the Taiwanese NHI program are CHM.[17] We only mention this because acupuncture has become the popular modality of complementary therapies, as perceived by patients or physicians, in the west.[26,27] From our results, however, it is evident that Taiwanese CM physicians perceive herbs as an indispensable part of treatment.

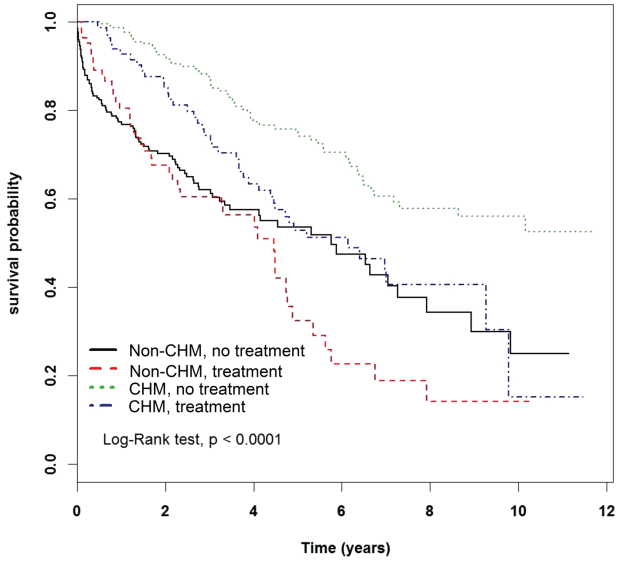

FIGURE 2. Kaplan–Meier curves of overall survival in patients with chronic lymphoid leukemia according to use of Chinese Herbal Medicine (CHM) and standard treatment.CHM = Chinese Herbal Medicine, Treatment = Western medical treatment.

Our most significant finding was the reduced risk of mortality associated with the utilization of CHM among CLL patients (0.4243, 95% CI 0.3233–0.5455, $P < 0.0001$). This was also reflected by a follow-up time that was longer by 42% in the CHM group than in the non-CHM group. In addition, in Table 3, it was demonstrated that the reduction in risk had a direct relation to the length of time CHM was directly related to the length of use of CHM. When examining the accumulated use of CHM, users in the ''30 to 180 days'' group were at less risk than those in the ''<30 days'' group, and the same was true for patients in the ''>180 days'' compared to the ''30 to 180 days'' group ($P < 0.001$). The fact that this improvement was dose-dependent strengthens the possibility of a causal relation between CHM and a decrease in HR. This reduction in HR is quite significant. For the sake of comparison, the trials from the German CLL study group published in 2010 showed that treatment-naive patients on the FCR regimen versus FC alone had an overall survival (OS) HR of 0.61 (95% CI 0.41–0.91, $P = 0.017$).[2]

One of the limitations of this study was that we had no information regarding the levels of fitness and health of patients. For example, these would be taken into consideration when choosing between a regimen of FCR, fludarabine plus

TABLE 3. Hazard Ratios and 95% Confidence Intervals of Mortality Risk Associated With Cumulative Use of Days of Chinese Herbal Medicine Among Chronic Lymphocytic Leukemia Patients

			Hazard Ratio (95% CI)	
	n	Frequency. of Mortality	Crude	Adjusted
Non-CM users or CHM users <30 days	416	177	1 (reference)	1 (reference)
CHM users (> = 30 days) ‡				
30–180 days	141	49	0.58 (0.42–0.80)***	0.57 (0.42–0.79)***
>180 days	59	15	0.35 (0.21–0.60)***	0.35 (0.21–0.60)***
P for trend			<0.0001	<0.0001

Crude HR represented relative hazard ratio; adjusted HR represented adjusted hazard ratio: mutually adjusted for age group, gender, urbanization level, hypertension, diabetes, congestive heart failure, chronic obstructive pulmonary disease, chronic kidney disorder, number of comorbidities (<2, ≥2), treatment and drugs used including fludarabine, rituximab, cyclophosphamide, and chlorambucil.

CHM = Chinese herbal medicine, CHM = Chinese Medicine, CI = confidence interval, HR = hazard ratio.

*$P < 0.05$.
**$P < 0.01$.
***$P < 0.001$.

TABLE 4. Hazard Ratios and 95% Confidence Intervals of Mortality Risk Associated With Cumulative Use of Herbal Formulas Among Chronic Lymphocytic Leukemia Patients

TCM Prescription		Mortality		Hazard Ratio (95% CI)	
		n	Frequency	Crude	Adjusted
Non-Chinese Herbal Medicine group		306	138		1 (reference)
Single-herb products					
Pin yin nomenclature	Scientific name				
Bai Hua She She Cao	*Hedyotis diffusa*	29	11	0.52 (0.28–0.97)*	0.48 (0.25–0.90)*
Yan Hu Suo	*Corydalis yanhusuo*	50	10	0.21 (0.11–0.40)***	0.22 (0.11–0.42)***
Bei Mu	*Fritillaria thunbergii*	56	19	0.40 (0.24–0.64)***	0.37 (0.23–0.61)***
Huang Qin	*Scutellaria baicalensis*	49	12	0.28 (0.16–0.51)***	0.29 (0.16–0.52)***
Dan Shen	*Salvia miltiorrhiza*	50	14	0.34 (0.19–0.59)***	0.34 (0.20–0.60)***
Ban Lan Gen	*Isatis tinctoria*	31	10	0.42 (0.22–0.79)***	0.40 (0.21–0.77)**
Ge Gen	*Pueraria lobata*	53	14	0.27 (0.16–0.47)***	0.27 (0.15–0.48)***
Ban Zhi Lian	*Scutellaria barbata*	12	6	0.72 (0.32–1.64)	0.77 (0.33–1.80)
Ju Hua	*Chrysanthemum morifolium*	23	8	0.39 (0.19–0.81)**	0.41 (0.20–0.84)*
Huang Qi	*Astragalus membranaceus*	46	11	0.26 (0.14–0.49)***	0.26 (0.14–0.49)***
Multiherb products					
Pin yin nomenclature	Scientific name				
Zhi Bo Di Huang Wan	–	37	6	0.19 (0.08–0.43)***	0.21 (0.09–0.47)***
Ma Zi Ren Wan	–	16	3	0.19 (0.06–0.60)**	0.19 (0.06–0.59)**
Shen Ling Bai Zhu San	–	18	5	0.29 (0.12–0.71)**	0.29 (0.12–0.71)**
Bu Zhong Yi Qi Tang	–	37	16	0.56 (0.34–0.95)*	0.55 (0.32–0.93)*
San Zhong Kui Jian Tang	–	18	5	0.39 (0.16–0.95)*	0.38 (0.15–0.93)*
Zhi Gan Cao Tang	–	42	12	0.32 (0.18–0.59)***	0.30 (0.17–0.55)***
Ping Wei San	–	36	16	0.58 (0.35–0.98)*	0.60 (0.35–1.01)
Gui Pi Tang	–	37	16	0.57 (0.34–0.96)*	0.54 (0.32–0.91)*
Jia Wei Xiao Yao San	–	42	5	0.15 (0.06–0.36)***	0.17 (0.07–0.41)***
Du Huo Ji Sheng Tang	–	43	8	0.20 (0.10–0.40)***	0.19 (0.09–0.39)***

Crude HR represented relative hazard ratio; adjusted HR represented adjusted hazard ratio: mutually adjusted for age group, gender, urbanization level, hypertension, diabetes, congestive heart failure, chronic obstructive pulmonary disease, chronic kidney disorder, number of comorbidities (<2, ≥2), treatment and drugs used including fludarabine, rituximab, cyclophosphamide, and chlorambucil.

CI = confidence interval.

*$P < 0.05$.
**$P < 0.01$.
***$P < 0.001$.

cyclophosphamide, or fludarabine alone.[28] Thus, the type of treatments may provide indirect insight into the levels of fitness and health of the patients. One seemingly suspicious finding in our study was that the CHM group and the non-CHM group had a follow-up time of 4.59 and 2.67 years, respectively. At first glance, we assumed that this was suggestive of an error in analyses, as western CLL patients often achieve much longer survival durations than these. However, it is important to note that life expectancy in Taiwan in 2011 was 75.94 for males and 82.60 for females, and was even lower during the preceding decade.[29] As the majority of patients in this cohort were male and roughly the age of 70, the follow-up times found are not inconceivable.

It has been shown that ~90% of newly diagnosed CLL patients suffer from 1 or more comorbidities.[30] However, thus far the only relation established between comorbidities and overall survival in CLL was reported in a recent analysis of the CLL4 and CLL5 trials, which showed that patients who suffered from 2 comorbidities or more had lower survival rates than those with <2.[31] Therefore, we chose to adjust our regression model according to this $<2/\geq 2$ cut point and found that the HR associated with the use of CHM was lower in both cases ($P < 0.001$, Table 2). We experimented with adjusting our regression model for the diseases in Table 1 and according to the Charlson Comorbidity Index. The differences in HR between the adjustment methods were negligible and the HR of the CHM group remained low in all cases.

An additional point of note is the homogeneity of our population. It has already been established that the disease course of CLL differs between ethnic groups.[32] Although studies have shown that CLL is on the rise in Taiwan, the prevalence of this disease is higher in Western countries. However, Taiwanese patients display much poorer survival rates than their American counterparts.[23,33] In a study conducted in the UK, Asian CLL patients' time-to-first-treatment was significantly shorter and overall survival rates lower when compared to those of Caucasians.[34] These differences make it difficult to infer the benefit that other ethnic groups would have from CHM treatment.

One further point to note is that the NHIRD does not contain information regarding performance status, staging, genetic mutations, molecular markers, and organ toxicity which all may confer to a favorable or unfavorable outcome. These are irreplaceable, however, we showed that the differences in baseline CCI score of patients from both groups was not significant and that in both groups, virtually the same amount of patients received HSCT.

An additional contribution of this study is the list of single-herb and multiherb products presented in Table 4. The prescription process of CHM differs from that of biomedicine in that there is not a 1:1 relationship between prescription and disorder, and the treatment of CLL may vary according to the symptoms and signs displayed by the patient. Although some of the herbs presented, for example, *Hedyotis diffusa* and *Salvia miltiorrhiza*, have been researched in the context of leukemia, other herbs such as *Corydalis yanhusuo* have not. Thus, the products listed in Table 4 may be used in future basic and clinical research.

Taking these limitations into consideration, this study has presented a reduction in the hazard ratio of CLL patients who received CHM. It is impossible to rule out certain influences such as patient motivation in this type of retrospective study; however, the results showed that reduction in HR was dose-dependent, and challenging the notion that the reduced HR was a result of other factors.

In conclusion, we supplied data including western medicine and CHM from a relatively large population that spanned over a significant amount of time. Overall, we can report novel data concerning the treatment of CLL with adjunctive CHM, which may have a substantial positive impact on the management of this disease, especially for treatment-naive patients. Alternative therapies and change of the social and environmental setting may have positive impact on health and course of diseases.[35] Further research is needed to substantiate whether this relationship holds true in non-Asian patients as well, and prospective studies are needed to confirm the causal relationship between CHM and the outcomes displayed.

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Hindawi Publishing Corporation
Evidence-Based Complementary and Alternative Medicine
Volume 2016, Article ID 8394850, 12 pages
http://dx.doi.org/10.1155/2016/8394850

Research Article

The Effectiveness of Traditional Chinese Medicine in Treating Patients with Leukemia

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Received 22 May 2016; Revised 15 August 2016; Accepted 14 September 2016

Academic Editor: Raffaele Capasso

Leukemia is the most common malignancy among all childhood cancers and is associated with a low survival rate in adult patients. Since 1995, the National Health Insurance (NHI) program in Taiwan has been offering insurance coverage for Traditional Chinese Medicine (TCM), along with conventional Western medicine (WM). This study analyzes the status of TCM utilization in Taiwan, in both pediatric and adult patients with leukemia. A retrospective cohort study was conducted using population-based National Health Insurance Research Database of Registry of Catastrophic Illness, involving patient data from 2001 to 2010 and follow-up data through 2011. The effectiveness of TCM use was evaluated. Relevant sociodemographic data showed that both pediatric and adult patients who were TCM users one year prior to leukemia diagnosis were more likely to utilize TCM services for cancer therapy. A greater part of medical expenditure of TCM users was lower than that of TCM nonusers, except little discrepancy in drug fee of adult patients. The survival rate is also higher in TCM users. Altogether, these data show that TCM has the potential to serve as an adjuvant therapy when combined with conventional WM in the treatment of patients with leukemia.

1. Introduction

Leukemia originates in the bone marrow and results in the production of a large number of abnormal white blood cells. The four main subtypes of leukemia are acute lymphoblastic leukemia (ALL), acute myelogenous leukemia (AML), chronic lymphocytic leukemia (CLL), and chronic myelogenous leukemia (CML) [1]. Leukemia is the most common malignancy diagnosed in children accounting for greater than 30% of all childhood cancers [2]. While ALL is the most prevalent cancer in childhood and also the first leading cause of death from cancer within 20 years of age [3], AML is more common in older adults [4]. Patients with leukemia may undergo chemotherapy or hematopoietic stem cell transplants, which are associated with massive physical suffering and economic burden [5, 6].

The National Health Insurance (NHI) program has offered insurance cover for Traditional Chinese Medicine (TCM) and conventional Western medicine (WM) since 1995. Several studies have demonstrated that TCM as adjuvant therapy can help improve the quality of life and alleviate the side effects associated with WM use. Importantly, it can enhance the efficacy of WM treatment against tumors and improve the survival rate [7–13]. For instance, one study indicated that TCM combined with chemotherapy significantly elevates survival rate and improves the quality of

life in patients with advanced non-small-cell lung carcinoma [12]. Another observational study demonstrated that TCM as adjuvant therapy helps to lower the risk of mortality relative to "TCM nonusers" in advanced breast cancer [9]. Apart from case reports and standardized questionnaire surveys, there are few large-scale studies on TCM use among leukemia patients [14, 15]. Thus, our study aimed to explore the determinants of TCM utilization in both pediatric and adult leukemia patients and further evaluate the overall survival of patients.

2. Materials and Methods

2.1. Research Data Sources. The NHI program, initiated in 1995, currently covers nearly 99.6% of the residents in Taiwan. The Bureau of National Health Insurance has contracts and cooperative agreements with nearly 97% of all hospitals and 92% of all clinics. This study included National Health Insurance Research Database (NHIRD) claim datasets that are safe from counterfeits due to the severe penalties involved [16]. The NHIRD datasets used in this study consisted of registry for beneficiaries, ambulatory and inpatient care claims, and registry for catastrophic illness from 1999 to 2011. Besides these, the NHIRD database contains demographic data, dates of visits, International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnostic codes, complete prescription details, and expenditure incurred by the beneficiaries. Data for detailed diagnoses and treatments provided by physicians were included. On the other hand, all cancer cases registered in the catastrophic illness database were eligible for an exemption from copayment. Our study was approved by the Joint Institutional Review Board of Public Health, Social and Behavioral Science Committee, China Medical University and Hospital.

2.2. Study Population. Our population-based retrospective cohort study included newly diagnosed patients with leukemia (ICD-9-CM code 204–208) identified from the registry of catastrophic illness between January 1, 2001, and December 31, 2010. In Taiwan health care system, the diagnosis of leukemia cases was done by WM physicians and cannot be done by TCM physicians because all diagnosis tests, including regular blood routine test (CBC/DC), blood smear (observing blood cell morphology), bone marrow biopsy (observing bone marrow cell morphology), and symptoms and signs, can be performed only by WM physicians. The index date was the initial date of leukemia diagnosis and all patients were followed up through December 31, 2011, or until the patients' death date within this interval or withdrawal from NHI. The index date was the date of first diagnosis. We analyzed 2,355 newly diagnosed pediatric patients (0–18 years old) and 10,208 newly diagnosed adult patients (19–80 years old) with leukemia. Patients who visited TCM physicians and used TCM at least once after being diagnosed with leukemia were deemed "TCM users" and the rest were deemed "TCM nonusers."

2.3. Comorbidities and Classification of Expenditures. This study considered TCM and WM ambulatory care, including dates of visit, date of birth, patient gender, medical facility and department visited, prescribing physician, dispensing pharmacist, three items from the ICD-9-CM codes, primary procedure, type of copayment, and paid amounts. We also analyzed the coexisting diseases in the leukemia patients based on the ICD-9-CM codes. Types of expenditure included fees for consultation, treatment and medical supplies, diagnosis fee, and drug fee.

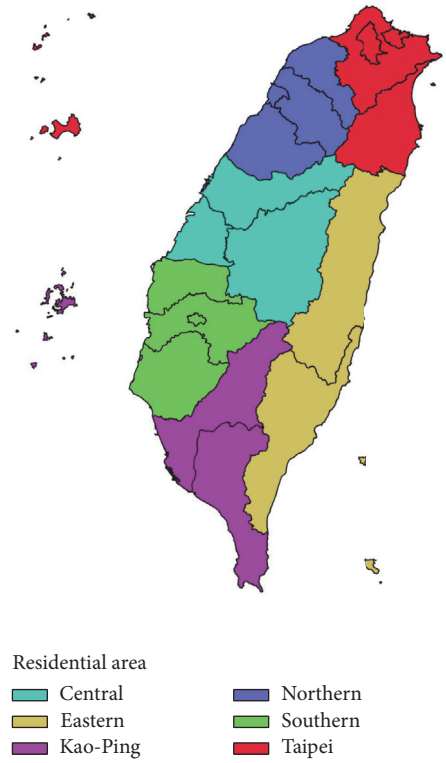

Figure 1: The residential areas of the study population.

2.4. Sociodemographic Factors and Urbanization Levels of Residential Area. The sociodemographic factors included age, gender, insurance premium amount, and the insured unit. Pediatric patients were further divided into 3 subgroups: 0–6, 7–12, and 13–18 years. Similarly, the adult patients were also divided into 3 subgroups: 19–40, 41–60, and 61–80 years. The amount of insurance premium, determined from the individual working salary, was classified into four levels: <20,000, 20,000–39,999, 40,000–59,999, and >60,000 NT$/month. The residential areas of the study population comprised 6 areas: Northern area, Taipei, Central area, Southern area, Eastern area, and Kao-Ping area (Figure 1). Furthermore, the urbanization level of the townships in Taiwan was categorized according to educational level of the population, population density, the ratio of elder people, and occupation in general [17]. The insured unit included government, school, private enterprise, occupational member, farmer and fishermen, low-income household, and veterans.

2.5. Statistical Analysis. All analyses were performed separately for the pediatric and adult patient groups. The

continuous variables were evaluated using means, standard deviations, and 95% confidence interval (CI), whereas categorical variables were evaluated using the numbers, percentages, and 95% CI. To compare the differences in continuous variables between TCM users and nonusers, Student's t-test was used, whereas Chi-square test was used to analyze the categorical variables. Furthermore, the adjusted odds ratio (OR), calculated using a multivariate logistic regression analysis, was used to explore the determinants of TCM utilization. The Kaplan-Meier estimator with a log-rank test was applied to evaluate the effect of TCM use on overall survival. Pairwise comparisons of overall survival among groups of no, low, and high TCM use were adjusted by Bonferroni correction. All p values were calculated using two-sided tests, and the threshold for statistical significance was set at $p < 0.05$. All analyses were performed using Statistical Analysis System (SAS) version 9.3 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Factors Associated with TCM Use. A total of 292 (12.40%) pediatric patients and 936 (9.17%) adult patients availed TCM outpatient services. In these leukemia patients, we observed that patients who were TCM users one year prior to the leukemia diagnosis and who resided in central area were more likely to utilize TCM services (Table 1). The mean numbers of days taking TCM in pediatric and adult leukemia patients were 184 (SD = 328) days and 107 (SD = 254) days, respectively. The mean outpatient department (OPD) visits for TCM in pediatric and adult leukemia patients were 20.3 (SD = 35.3) and 10.5 (SD = 22.8), respectively. The distributions of cancer type were similar between TCM users and nonusers in both pediatric and adult leukemia patients.

3.2. Medical Institutes. TCM users within pediatric leukemia patients engaged private hospitals more often for outpatient services than TCM pediatric nonusers (42.15% versus 38.70%). Similar trend was also seen within adult leukemia patients (36.17% versus 34.20%). On the contrary, private clinics were more often engaged for outpatient services by TCM nonusers of pediatric patients when compared to TCM users (41.37% versus 35.22%) as well as by TCM adult nonusers (43.32% versus 41.13%) (Table 2).

3.3. Coexisting Diseases. We observed that lymphoid leukemia and myeloid leukemia were the two major diagnoses in these leukemia patients. Lymphoid leukemia was common in children and myeloid leukemia was diagnosed mainly in adults. Acute upper and lower respiratory infections were commonly diagnosed in both pediatric and adult patients, irrespective of TCM use by the patients (Table 3).

3.4. Expenditures. According to our analysis, drug fee was the major component of all outpatient medical expenditures (Table 4). For both pediatric and adult leukemia patients, the average cost of total amount per visit was higher for TCM users than that of TCM nonusers. In adult leukemia patients, the average cost of drug fee per visit in TCM users was higher than that of TCM nonusers. Nevertheless, the differences in average costs between these two groups were indeed minimal (2,557.98 NT$ versus 2,535.07 NT$). The costs of other items per visit in TCM users in adult leukemia patients were significantly lower than those of TCM nonusers, including fees for consultation, treatment, medical supply, and diagnosis fee. In pediatric patients, the average cost per visit in TCM users was consistently higher than that of TCM nonusers for all items including fees for consultation, treatment, medical supply, diagnosis fee, and drug fee.

3.5. Most Commonly Prescribed TCM Single and Formula Products. Details of the TCM single and formula products most frequently prescribed by TCM physicians are shown in Table 5. In pediatric leukemia patients, *Radix Astragali membranaceus* was the most commonly prescribed TCM single product, followed by *Bulbus Fritillariae thunbergii*, and *Herba Hedyotis diffusa*. Moreover, Xiang Sha Liu Jun Zi Tang was the most frequently prescribed TCM formula product, followed by Yu Ping Feng San and Zuo Gui Wan. The top three most commonly used TCM single products for adult leukemia patients were as follows, from the most common to the least: *Radix Astragali membranaceus, Radix et Rhizoma Salviae miltiorrhizae*, and *Fructus Ligustri Lucidi*. Moreover, the top three most commonly prescribed TCM single products were Gui Pi Tang, Liu Wei Di Huang Wan, and Zuo Gui Wan.

3.6. Overall Survival. We found that the overall survival rate was higher in TCM users compared to TCM nonusers in both pediatric and adult patients with leukemia (both $p < 0.001$) (Figure 2). During the 10 years that we followed, both pediatric and adult patients with leukemia who were TCM users had near 10% higher survival probability in comparison to the corresponding group of TCM nonusers patients. To further examine whether the overall survival rates were influenced by the number of days taking TCM and number of OPD visits for TCM use, we categorized these two variables using their median values as cutoff points (Figures 3 and 4). We observed that the overall survival rates were significantly different in subgroups of number of days taking TCM and OPD visits for TCM use in both pediatric and adult patients with leukemia (all $p < 0.001$). We observed a dose-response relationship among three subgroups of TCM use according to either patients with number of days taking TCM or number of OPD visits for TCM use. The highest overall survival rates were found in patients with high number of days taking TCM (≥42.5 for pediatric patients and ≥28 for adult patients), which were significantly higher than those with low number of days taking TCM (<42.5 for pediatric patients and <28 for adult patients) ($p = 0.0049$ for pediatric patients and $p < 0.0001$ for adult patients) and were also significantly higher than those who were TCM nonusers (both $p < 0.001$ for pediatric and adult patients). The differences in overall survival curves were different between patients with low number of days taking TCM and TCM nonusers ($p = 0.0051$ and <0.001 for pediatric and adult patients, resp.). Similarly, we observed significant pairwise differences in

Table 1: Sociodemographic factors of pediatric and adult patients with leukemia according to use of TCM.

Characteristic	Pediatric (N = 2,355)					Adult (N = 10,208)				
	TCM users		TCM nonusers		Adjusted OR‡ (95% CI)	TCM users		TCM nonusers		Adjusted OR‡ (95% CI)
	N	%	N	%		N	%	N	%	
Number of patients	292		2,063			936		9,272		
Age, years										
0–6	139	47.60	1,016	49.25	1.00					
7–12	89	30.48	480	23.27	1.10 (0.81–1.50)					
13–18	64	21.92	567	27.48	0.64 (0.46–0.89)**					
19–40						274	29.27	2,199	23.72	1.00
41–60						379	40.38	3,012	32.48	0.95 (0.80–1.13)
61–80						284	30.34	4,061	43.80	0.60 (0.48–0.70)***
Means (SD)	8.03	(5.07)	8.41	(5.65)		51.26	(15.67)	55.39	(17.24)	
Gender										
Female	129	44.18	843	40.86	1.00	428	45.73	3,740	40.34	1.00
Male	163	55.82	1,220	59.14	0.83 (0.64–1.07)	508	54.27	5,532	59.66	0.86 (0.74–0.99)*
TCM use one year prior to leukemia diagnosis										
TCM nonusers	180	61.64	1,523	73.82	1.00	437	46.69	6,048	65.23	1.00
TCM users	112	38.36	540	26.18	1.62 (1.23–2.13)***	499	53.31	3,224	34.77	1.97 (1.71–2.26)***
Insured amount (NT$/month)										
<20,000	286	97.95	2,035	98.64	1.00	610	65.17	6,736	72.65	1.00
20,000–39,999	6	2.05	27	1.31	2.02 (0.79–5.15)	197	21.05	1,613	17.40	1.23 (1.02–1.47)*
40,000–59,999	0	0.00	1	0.05	—	101	10.79	735	7.93	1.48 (1.15–1.90)**
≥60,000	—	—	—	—	—	28	2.99	188	2.03	1.65 (1.08–2.55)*
Urbanization										
Level 1 (highest)	78	26.71	564	27.34	1.00	278	29.70	2,521	27.19	1.00
Level 2	97	33.22	655	31.75	0.85 (0.59–1.24)	279	29.81	2,698	29.10	0.86 (0.70–1.04)
Level 3	48	16.44	371	17.98	0.52 (0.32–0.82)**	149	15.92	1,625	17.53	0.67 (0.53–0.85)***
Level 4	45	15.41	296	14.35	0.63 (0.39–1.02)	134	14.32	1,329	14.34	0.74 (0.58–0.96)*
Level 5 (lowest)	24	8.22	177	8.58	0.63 (0.34–1.14)	96	10.26	1,098	11.84	0.69 (0.51–0.94)*

Table 1: Continued.

Characteristic	Pediatric (N = 2,355)					Adult (N = 10,208)				
	TCM users		TCM nonusers		Adjusted OR‡ (95% CI)	TCM users		TCM nonusers		Adjusted OR‡ (95% CI)
	N	%	N	%		N	%	N	%	
Residential area										
Northern	32	10.96	304	14.74	1.00	85	9.08	1,245	13.43	1.00
Taipei	75	25.68	750	36.35	0.76 (0.46–1.24)	274	29.27	229	34.83	1.01 (0.77–1.34)
Central	104	35.62	306	14.83	3.33 (2.12–5.23)***	265	28.31	1,623	17.51	2.41 (1.85–3.14)***
Southern	36	12.33	324	15.71	1.17 (0.69–1.99)	163	17.41	1,372	14.80	1.95 (1.47–2.59)***
Eastern	3	1.03	42	2.04	0.73 (0.21–2.58)	27	2.88	261	2.82	1.78 (1.11–2.84)*
Kao-Ping	42	14.38	337	16.34	1.16 (0.70–1.92)	122	13.03	1,541	16.62	1.13 (0.84–1.52)
Insured unit										
Government, school employees	39	13.59	176	9.30	1.00	130	13.92	1,056	11.42	1.00
Private enterprise employees	145	50.52	916	48.39	0.70 (0.47–1.05)	404	43.25	3,533	38.21	0.91 (0.73–1.13)
Occupational member	37	12.89	342	18.07	0.47 (0.28–0.77)**	198	21.20	1,973	21.34	0.87 (0.68–1.12)
Farmers, fishermen	36	12.54	226	11.94	0.69 (0.40–1.18)	141	15.10	1,827	19.76	0.80 (0.60–1.07)
Low-income households and veterans registered in local government agency	30	10.45	233	12.31	0.58 (0.34–0.98)	61	6.53	857	9.27	0.73 (0.52–1.02)
Number of days taking TCM, means (SD)	184	(328)	—	—		107	(254)	—	—	
OPD visits for TCM, means (SD)	20.3	(35.3)	—	—		10.5	(22.8)	—	—	
Cancer subtype										
Lymphoid leukemia	205	70.21	1,377	66.75	1.00	217	23.18	1,896	20.45	1.00
Myeloid leukemia	79	27.05	609	29.52	1.10 (0.83–1.44)	649	69.34	6,670	71.94	0.85 (0.72–1.00)
Uncertain	8	2.74	77	3.73	0.88 (0.42–1.85)	70	7.48	706	7.61	0.87 (0.65–1.15)

ICD-9-CM: lymphoid leukemia, 204.xx; myeloid leukemia, 205.xx.

TCM: Traditional Chinese Medicine; OR: odd ratio; SD: standard deviation; CI: confidence interval; OPD: outpatient department.

*$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$.

‡Adjusted ORs were from the model considering age, gender, visit one year ago, insured amount, urbanization, residential area, and insured unit.

Table 2: Distributions of outpatient service providers for pediatric and adult patients with leukemia during 2001–2011.

Outpatient services providers	TCM users		TCM nonusers		p value for χ^2
	Visits	Percentage (95% CI)	Visits	Percentage (95% CI)	
Pediatric					
Type of provider					<0.001
Public hospitals	20,407	22.33 (22.06, 22.6)	80,522	19.47 (19.35, 19.59)	
Public Chinese medicine hospitals	20	0.02 (0.01, 0.03)	92	0.02 (0.02, 0.03)	
Private hospitals	38,522	42.15 (41.83, 42.47)	160,049	38.70 (38.55, 38.85)	
Private Chinese medicine hospitals	86	0.09 (0.07, 0.11)	191	0.05 (0.04, 0.05)	
Public clinics	160	0.18 (0.15, 0.2)	1,497	0.36 (0.34, 0.38)	
Private clinics	32,187	35.22 (34.91, 35.53)	171,108	41.37 (41.22, 41.52)	
Other medicine service providers	9	0.01 (0, 0.02)	103	0.02 (0.02, 0.03)	
Total	91,391		413,562		
Adult					
Type of provider					<0.001
Public hospitals	52,167	20.64 (20.49, 20.80)	354,202	19.77 (19.71, 19.83)	
Public Chinese medicine hospitals	400	0.16 (0.14, 0.17)	905	0.05 (0.05, 0.05)	
Private hospitals	91,396	36.17 (35.98, 36.36)	612,655	34.20 (34.13, 34.27)	
Private Chinese medicine hospitals	614	0.24 (0.22, 0.26)	4,044	0.23 (0.22, 0.23)	
Public clinics	3,782	1.5 (1.45, 1.54)	40,716	2.27 (2.25, 2.29)	
Private clinics	103,932	41.13 (40.94, 41.32)	776,052	43.32 (43.24, 43.39)	
Other medicine service providers	399	0.16 (0.14, 0.17)	3,026	0.17 (0.16, 0.17)	
Total	252,690		1,791,600		

TCM: Traditional Chinese Medicine; CI: confidence interval.

overall survival function among three subgroups of TCM use based on number of OPD visits.

4. Discussion

This study investigated the potential of TCM use as an adjuvant therapy for leukemia patients, both pediatric and adult, in Taiwan undergoing treatment with WM. The determinants for TCM utilization for leukemia patients in Taiwan, such as medical expenditure, and therapeutic effects were only scarcely reported in the past [18]. Our study shows that the combination therapy using TCM and WM for patients with leukemia does not cause additional financial burden relative to using WM only. Importantly, TCM use is associated with longer survival.

We observed that TCM utilization was more prevalent in pediatric leukemia patients rather than adults. We assume that children can barely tolerate the extremely uncomfortable symptoms and feelings accompanying chemotherapy, as previously suggested [19]. Studies show that TCM can alleviate adverse effects of WM and improve quality of life in cancer patients [7, 10, 11, 13]. Andersen's health behavior model, which is advocated by many scholars of sociology and public health, claims that the use of health services is determined by predisposing factors, enabling factors, and need factors [20]. In our study, significant factors for TCM use included predisposing factors of gender and health beliefs, such as TCM use one year prior to leukemia diagnosis. Enabling factors observed were height of medical insurance, residential area, and urbanization level, which were similar to those reported by Liao et al. [21, 22]. On the other hand, a particularly higher prevalence of TCM utilization was observed in central Taiwan, which has the highest per capita ratio of TCM physicians.

Radix Astragali membranaceus and *Fructus Ligustri Lucidi* were in the top 3 herbs for adult users and *Radix Astragali membranaceus* was the top one herbs for pediatric users. Both of these herbs have a function that increases white blood cell count [23]. Due to the indication of leukemia being a consistently elevated white blood cell count, some physicians thought using the herbs that increase white blood cell count is not recommended because of the potential exacerbation of leukemia. Given the findings of the present study, these herbs may increase healthy WBC without aggravating the leukemia. This can be supported by the prior studies of these two herbs demonstrating that they bolster host immune response for cytotoxic activity by promoting apoptosis of tumor cells and may help the recovery from chemotherapy or radiation treatments [18, 24–27]. The findings of the present study provide important information for TCM physicians and patients with leukemia.

The National Health Insurance program was started on March 1, 1995. In 2011, 22.60 million out of 22.96 million Taiwan residents were enrolled in this program. The comprehensive NHI database is considered an appropriate source to assess certain diseases. In addition, the NHI database provides abundant sample population size and details in studies, eliminating the bias associated with a limited sample size.

Our study has several limitations, though. Firstly, some patients visiting TCM physicians preferred to receive decoction formulations of Chinese medicine, which were self-paid

Table 3: Top 5 disease codes among pediatric and adult leukemia patients during the years 2001–2011 for all outpatients visits.

Ranking	TCM users			TCM nonusers		
	Disease (Code)	Number	Percentage (95% CI)	Disease (Code)	Number	Percentage (95% CI)
Pediatric						
Total visits	91,391			413,562		
1	Lymphoid leukemia (204)	36,529	39.97 (39.65, 40.29)	Lymphoid leukemia (204)	138,518	33.49 (33.35, 33.64)
2	Myeloid leukemia (205)	7,801	8.54 (8.35, 8.72)	Acute upper respiratory infections (465)	45,756	11.06 (10.97, 11.16)
3	Acute upper respiratory infections (465)	6,873	7.52 (7.35, 7.69)	Myeloid leukemia (205)	34,551	8.35 (8.27, 8.44)
4	Leukemia of unspecified cell type (208)	4,698	5.14 (5, 5.28)	Acute bronchitis and bronchiolitis (466)	15,506	3.75 (3.69, 3.81)
5	Acute bronchitis and bronchiolitis (466)	2,962	3.24 (3.13, 3.36)	Acute sinusitis (461)	12,141	2.94 (2.88, 2.99)
Adult						
Total visits	252,690			1,791,600		
1	Myeloid leukemia (205)	55,031	21.78 (21.62, 21.94)	Myeloid leukemia (205)	264,653	14.77 (14.72, 14.82)
2	Lymphoid leukemia (204)	19,336	7.65 (7.55, 7.76)	Acute upper respiratory infections (465)	97,491	5.44 (5.41, 5.47)
3	Acute upper respiratory infections (465)	11,117	4.4 (4.32, 4.48)	Lymphoid leukemia (204)	76,117	4.25 (4.22, 4.28)
4	Gingival and periodontal diseases (523)	5,680	2.25 (2.19, 2.31)	Diabetes mellitus (250)	56,042	3.13 (3.1, 3.15)
5	Diseases of hard tissues of teeth (521)	5,123	2.03 (1.97, 2.08)	Essential hypertension (401)	53,009	2.96 (2.93, 2.98)

TCM: Traditional Chinese Medicine; CI: confidence interval.

Table 4: Expenditures for outpatient services for pediatric and adult leukemia patients (NT$) during the period 2001–2011.

Characteristic	TCM users			TCM nonusers			t value
	Total	Percentage (95% CI)	Average cost per visit (95% CI)	Total	Percentage (95% CI)	Average cost per visit (95% CI)	
Pediatric							
Outpatient visits	91,391			413,562			
Fees for consultation, treatment, and medical supplies	52,088,100	38.09 (38.08, 38.1)	569.95 (559.62, 580.28)	245,838,958	32.74 (32.73, 32.74)	594.45 (589.71, 599.19)	4.22***
Diagnosis fee	19,341,052	14.14 (14.14, 14.15)	211.63 (210.86, 212.4)	88,180,707	11.74 (11.74, 11.74)	213.22 (212.84, 213.61)	3.64***
Drug fee	65,311,809	47.76 (47.75, 47.77)	714.64 (680.14, 749.15)	416,969,010	55.52 (55.52, 55.53)	1008.25 (986.8, 1029.7)	14.16***
Total amount	136,740,961	100	1496.22 (1459.61, 1532.83)	750,988,675	100	1815.92 (1793.74, 1838.1)	14.64***
Adult							
Outpatient visits	252,690			1,791,600			
Fees for consultation, treatment, and medical supplies	170,260,064	19.55 (19.55, 19.56)	673.79 (663.88, 683.70)	1,282,955,508	20.66 (20.66, 20.66)	716.10 (711.68, 720.52)	7.64***
Diagnosis fee	54,059,202	6.21 (6.21, 6.21)	213.93 (213.46, 214.41)	386,270,204	6.22 (6.22, 6.22)	215.60 (215.42, 215.78)	6.46***
Drug fee	646,375,253	74.24 (74.23, 74.24)	2557.98 (2512.05, 2603.91)	4,541,817,387	73.12 (73.12, 73.13)	2535.07 (2516.85, 2553.29)	−0.91
Total amount	870,694,519	100	3445.70 (3398.59, 3492.81)	6,211,043,099	100	3466.77 (3447.99, 3485.55)	0.81

*** $P < 0.001$.

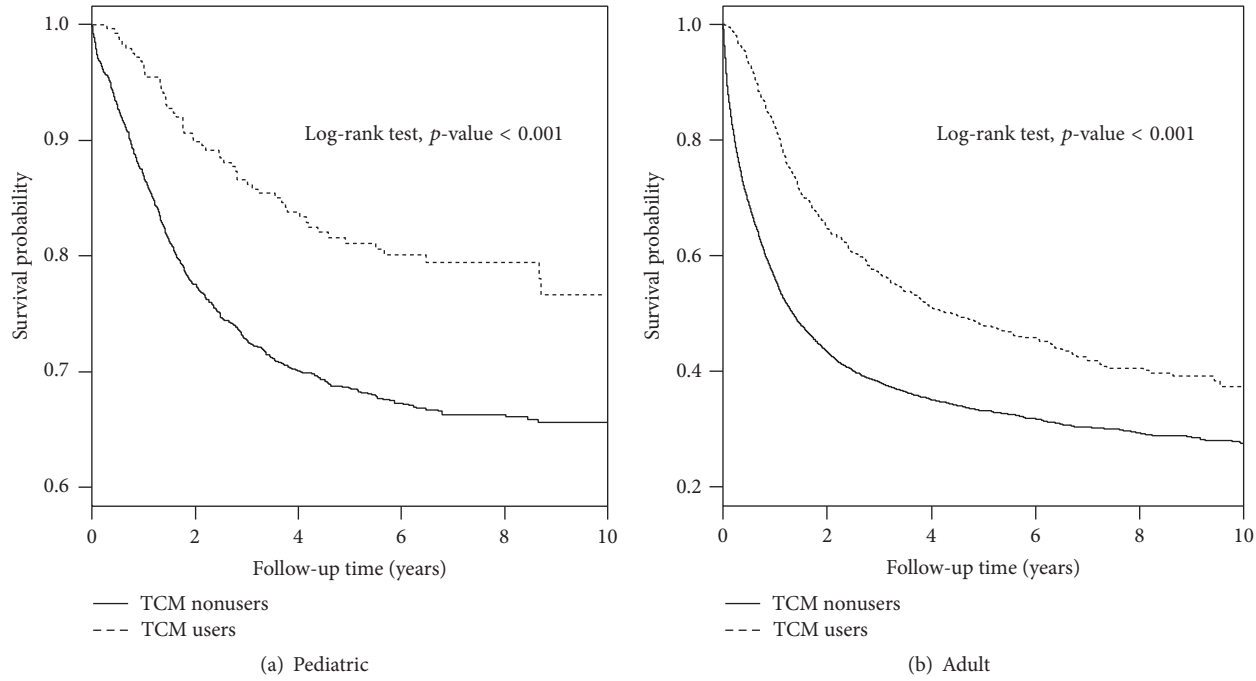

Figure 2: Kaplan-Meier curves of overall survival in patients with leukemia based on TCM use during the follow-up period.

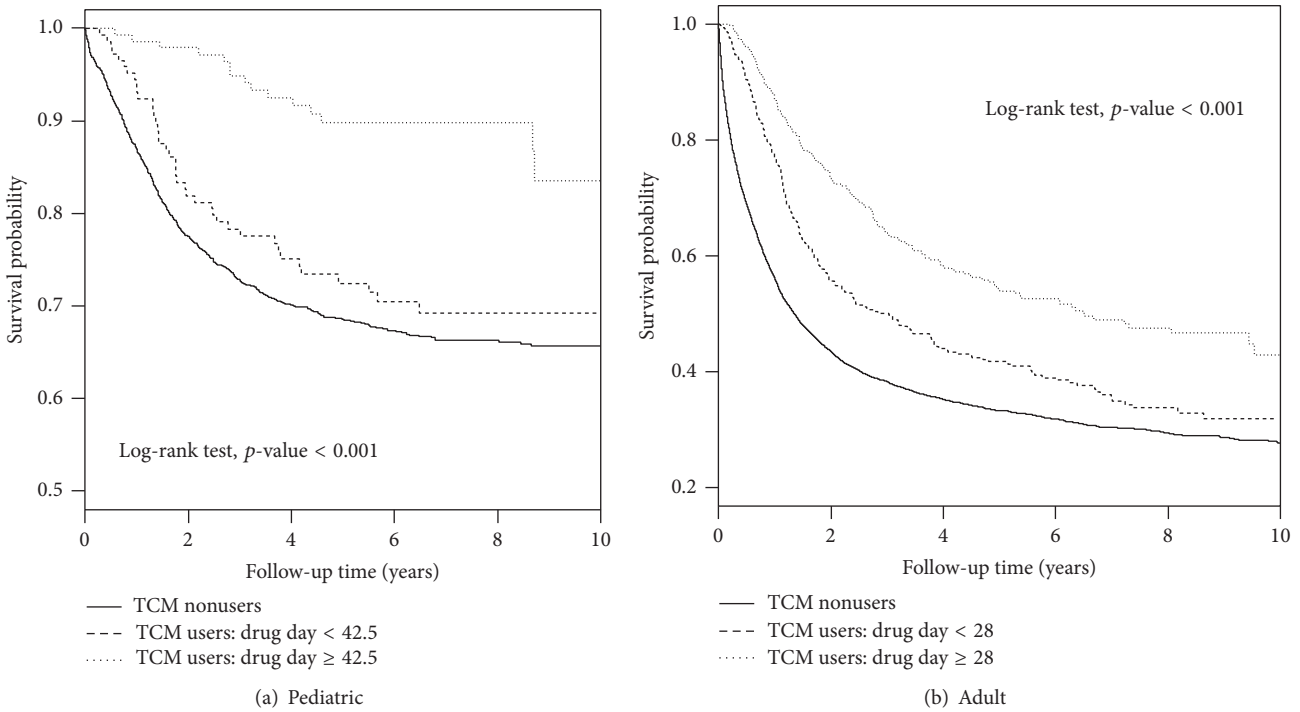

Figure 3: Kaplan-Meier curves of overall survival in patients with leukemia based on number of drug days for TCM use during the follow-up period. (a) TCM nonusers versus TCM user: days taking TCM < 42.5, $p = 0.0051$. TCM nonusers versus TCM user: days taking TCM ≥ 42.5, $p < 0.001$. TCM user: days taking TCM < 42.5 versus TCM user: days taking TCM ≥ 42.5, $p = 0.0049$. (b) TCM nonusers versus TCM user: days taking TCM < 28, $p < 0.001$. TCM nonusers versus TCM user: days taking TCM, $p < 0.001$. TCM user: days taking TCM < 28 versus TCM user: days taking TCM ≥ 28, $p = 0.0001$.

Table 5: Top ten formula CHPs and single CHPs prescribed by TCM physicians to treat pediatric and adult patients with leukemia in Taiwan, 2000–2011.

	Single CHPs		Formula CHPs	
	Name	Number, frequency (%)	Name	Number, frequency (%)
Pediatric	*Radix Astragali membranaceus*	103 (5.80)	Xiang Sha Liu Jun Zi Tang	36 (7.86)
	Bulbus Fritillariae thunbergii	87 (4.90)	Yu Ping Feng San	27 (5.90)
	Herba Hedyotis diffusa	74 (4.16)	Zuo Gui Wan	25 (5.46)
	Radix Scutellariae baicalensis	65 (3.66)	Bu Zhong Yi Qi Tang	24 (5.24)
	Radix Puerariae lobatae	57 (3.21)	Shen Ling Bai Zhu San	20 (4.37)
	Radix Glycyrrhizae uralensis	52 (2.93)	Bao He Wan	18 (3.93)
	Herba Houttuyniae cordata	45 (2.53)	Xin Yi San	16 (3.49)
	Semen Ziziphi Spinosi	34 (1.91)	Ma Zi Ren Wan	16 (3.49)
	Rhizoma Polygonati odorati	32 (1.80)	Liu Wei Di Huang Wan	14 (3.06)
	Herba Scutellariae barbatae	29 (1.63)	Ge Gen Tang	14 (3.06)
Adult	*Radix Astragali membranaceus*	173 (4.07)	Gui Pi Tang	83 (6.18)
	Radix et Rhizoma Salviae miltiorrhizae	133 (3.13)	Liu Wei Di Huang Wan	53 (3.95)
	Fructus Ligustri Lucidi	108 (2.54)	Zuo Gui Wan	39 (2.91)
	Sargentodoxa Cuneata	86 (2.02)	Gui Lu Er Xian Jiao	39 (2.91)
	Herba Hedyotis diffusa	82 (1.93)	Sheng Mai San	36 (2.68)
	Rhizoma Dioscoreae polystachya	71 (1.67)	Jia Wei Xiao Yao San	35 (2.61)
	Bulbus Fritillaria thunbergii	69 (1.62)	Xue Fu Zhu Yu Tang	27 (2.01)
	Cortex Lycii Radicis	63 (1.48)	Xiang Sha Liu Jun Zi Tang	26 (1.94)
	Radix Glycyrrhizae uralensis	59 (1.39)	Xin Yi Qing Fei Tang	25 (1.86)
	Semen Ziziphi Spinosae	58 (1.36)	Ren Shen Yang Rong Tang	24 (1.79)

TCM: Traditional Chinese Medicine; CHPs: Chinese herb products.

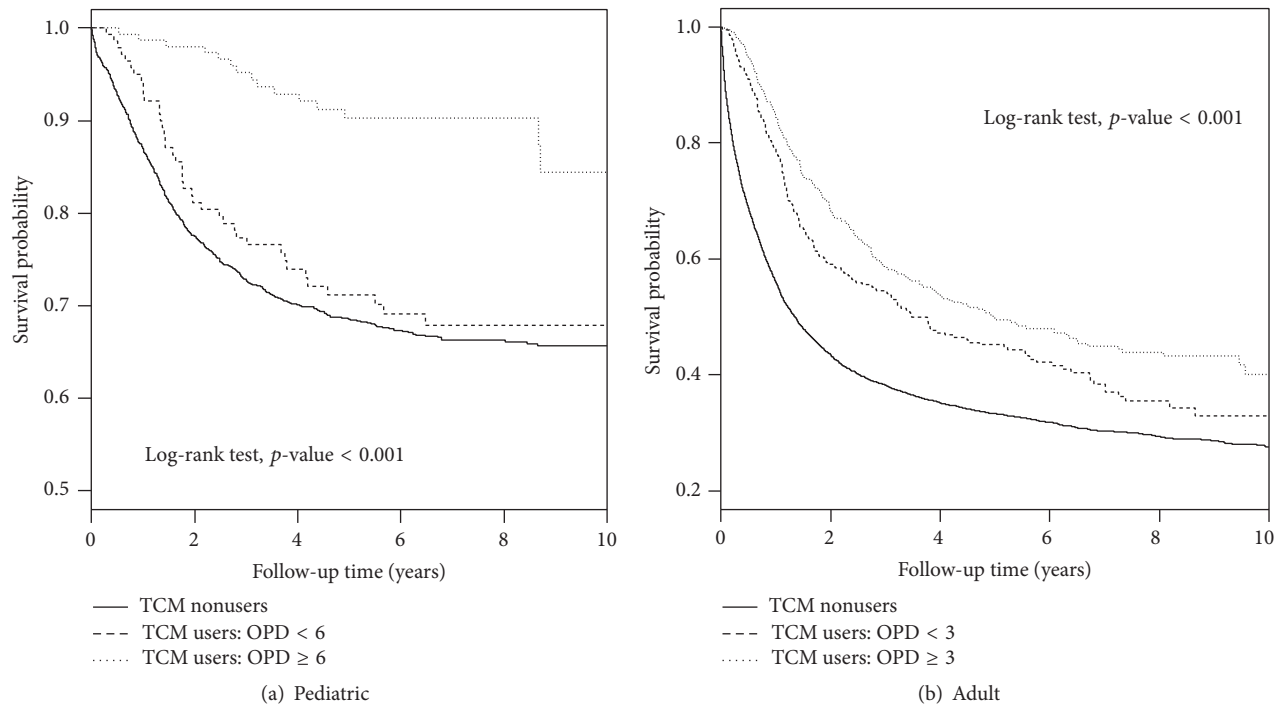

Figure 4: Kaplan-Meier curves of overall survival in patients with leukemia based on number of outpatient department (OPD) visits for TCM use during the follow-up period. (a) TCM nonusers versus TCM user: OPD < 6, $p = 0.0075$; TCM nonusers versus TCM user: OPD ≥ 6, $p < 0.001$; TCM user: OPD < 42.5 versus TCM user: OPD ≥ 6, $p = 0.0009$. (b) TCM nonusers versus TCM user: OPD < 3, $p < 0.001$; TCM nonusers versus TCM user: OPD ≥ 3, $p < 0.001$; TCM user: OPD < 3 versus TCM user: OPD ≥ 3, $p < 0.001$.

and not covered by the NHI program. In addition, about 10% of the TCM clinics were not contracted to the NHI because of the low reimbursement rates provided by the NHI. Therefore, the prevalence of TCM use and costs of outpatient visits could be underestimated. Secondly, we only explored the efficacy of general TCM utilization, including overall survival, but we did not consider the subtypes of leukemia and TCM prescriptions, which should be investigated in further studies. Last, the database does not contain information on daily activity, dietary habits, and body mass index, which may also be factors for TCM utilization and health care costs. Further studies considering the above information are therefore warranted.

5. Conclusion

Our study investigated the TCM utilization and prevalence among pediatric and adult patients with leukemia in Taiwan. It shows that TCM as adjuvant therapy combined with WM may indeed alleviate adverse symptoms, improve quality of life, and prolong overall survival, without incurring excess medical expenditure. This line of study in the future should aim at ruling out the possible confounders such as diet, lifestyle behaviors of exercise, and psychological status. The results of our study could be useful to health-policy decision makers as well as clinical practitioners while considering the integration of TCM with WM.

Competing Interests

The authors declare that there is no conflict of interests regarding the publication of this manuscript.

Authors' Contributions

Yu-Jun Wang and Chung-Chih Liao contributed equally to this work.

Acknowledgments

The Taiwan Ministry of Health and Welfare Clinical Trial and Research Center of Excellence (MOHW105-TDU-B-212-133019), China Medical University Hospital, Academia Sinica Taiwan Biobank Stroke Biosignature Project (BM10501010037), NRPB Stroke Clinical Trial Consortium (MOST 105-2325-B-039-003), Tseng-Lien Lin Foundation, Taichung, Taiwan, Taiwan Brain Disease Foundation, Taipei, Taiwan, and Katsuzo and Kiyo Aoshima Memorial Funds, Japan, supported this study.

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Aromatase Inhibitors: Anastrozole/Arimidex & Exemestane/Aromasin

Aromatase Inhibitors are estrogen blockers that works by inhibiting aromatase enzymes. Aromatase enzymes are found in the body's muscle, skin, breast and fat and are used to convert androgens (hormones produced by the adrenal glands) into estrogens. Arimidex & Aromasin are approved as first-line treatment of postmenopausal women with hormone receptor-positive locally advanced or metastatic breast cancer. It is second line in advanced breast cancer in postmenopausal women with disease progression following tamoxifen therapy. It is taken orally either with or without food on a daily basis.

Common side effects (occurring in greater than 30%) include; Hot Flashes, Muscle/Joint pain and Stomach upset. Less common side effects (occurring in about 10-29%) include; fatigue, mood disturbance, depression, osteoporosis, back pain, carpal tunnel, insomnia, hypertension, sore throat, nausea, vomiting, rash, dyspnea, lymphedema, peripheral edema.[iii] Women who have a history of blockage in their heart arteries who take Anastrazole/Arimidex may have an increase in symptoms of decreased blood flow to their heart compared to similar women who take tamoxifen. In women with pre-existing ischemic heart disease, the incidence of ischemic cardiovascular events was 17% in patients on Anastrazole/Arimidex and 10% in patients on tamoxifen.[iii] Joint pain that occurs in the first 6 weeks while on Aromatase Inhibitors typically worsens over time vs resolving.[iv] In one study, 32% of women with early breast cancer discontinued Aromatase Inhibitors within 2 years due to side effects, 24% of these due to joint pain specifically.[v]

Herbal Interactions with Anastrazole/Arimidex: In a double blind RCT, addition of ground flaxseeds to anastrozole did not impact excretion of anastrozole.[vi] Women treated with tamoxifen, anastrozole or letrozole safely took gingko biloba 120mg twice daily without impacting plasma levels of their medication.[vii]

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Knowledge in Naturopathic Oncology Website

Supportive Care Considerations for AI Arthralgia

Homeopathics: In KNOW, you can find a controlled trial, women with breast cancer who were planning to start treatment with an aromatase inhibitor, the patients taking a combination of homeopathic Ruta graveolens 5CH and Rhus toxicodendron 9CH twice daily for 3 months experienced less joint pain compared to women who did not receive the homeopathic treatment.[viii]

CE question: After 3 months, 5% of women taking the homeopathic combination had a significantly worse composite pain score, compared to how many women not taking homeopathics?

CE Question: After 3 months, 5% of women on the homeopathics increased their pain medication, compared to 45% of women not taking homeopathics.

B12: In KNOW, you can find a phase II study, women with breast cancer who were experiencing joint pain on aromatase inhibitors, daily sublingual vitamin B12 significantly reduced their pain scores.[ix]

CE Question: What dose of B12 was used in this trial?

CE Question: When B12 was given to women with average and severe joint pain levels, how much did their pain improve?

CE Question: Homocysteine and methylmalonic acid levels both were reduced after B12 supplementation

Glucosamine/Chondroitin: In KNOW, you can find a phase II study, women with breast cancer who were experiencing joint pain on aromatase inhibitors who took glucosamine-sulfate + chondroitin-sulfate experienced moderate symptom relief.[x]

CE Question: What dose of glucosamine/chondroitin was used to reduce aromatase inhibitor arthralgia?

CE Question: At 12 weeks, over half of participants had ≥20 % decrease in their hip and knee pain, and less hand and wrist pain.

CE Question: Joint pain relief from glucosamine + chondroitin lasted until the end of the study at 24 weeks

Vitamin D: In KNOW, you can find a double-blind RCT, adding high dose vitamin D2 supplementation to women taking Anastrozole improved aromatase inhibitor-induced musculoskeletal symptoms and bone loss.[xi]

CE Question: ***High dose (****50,000IU Vitamin D2 weekly for 16 weeks, then monthly for 2 months) was more effective at reducing joint pain than low dose (50,000IU Vitamin D2 weekly for 8 weeks then monthly for 4 months) or placebo.*

CE Question: Weekly high doses of Vitamin D2 were found to be effective at reducing only joint pain, not muscle pain

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