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Effect of the Botanical Compound LCS101 on Chemotherapy-Induced Symptoms in Patients with Breast Cancer: A Case Series Report

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Abstract: The treatment of breast cancer invariably results in severe and often debilitating symptoms that can cause significant distress and severely impair daily function and quality-of-life (QOL). We treated a series of 20 female breast cancer patients with the botanical compound LCS101 as adjuvant to conventional chemotherapy. At the end of the treatment regimen, patients rated their symptoms. 70% reported that they had either no or mildly severe levels of fatigue; 60% none to mildly severe weakness; 85% none to mildly severe pain; 70% none to mildly severe nausea; and 80% none to mildly severe vomiting. Only 20% reported severe impairment of overall function, and only 40% severely impaired QOL. No toxic effects were attributed by patients to the LCS101 treatment, and 85% reported that they believed the botanical compound had helped reduce symptoms. The effects of LCS101 on clinical outcomes in breast cancer should be tested further using randomized controlled trials.

Keywords: breast cancer, fatigue, nausea and vomiting, pain, quality-of-life, botanical compounds

Integrative Medicine Insights 2013:8 1–8

doi: [10.4137/IMI.S10841](https://doi.org/10.4137/IMI.S10841)

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Introduction

Breast cancer remains a major cause of morbidity and mortality, with one in eight women being diagnosed with this disease during their lifetime.¹ Treatment of breast cancer entails surgery, radiation and chemotherapy, with more than half of patients undergoing treatment with agents such as anthracyclines and taxanes.² Cancer treatments invariably lead to significant and potentially debilitating symptoms such as fatigue and weakness, pain, and chemotherapy-induced nausea and vomiting (CINV).³⁻⁵ Pain and fatigue often overlap, and both are associated with the patient's mental health.^{3,4} Most chemotherapy agents are at least moderately emetogenic, necessitating the use of antiemetic agents.⁵ Treatment-related symptoms can significantly impair overall function and quality-of-life (QOL) parameters for these patients.⁶

Most patients with breast cancer (60%–70%) report using at least one form of complementary medicine (CM) during their illness.⁷ Herbal medicine is one of the most popular CM therapies in use, and botanical compounds are perceived by patients to be both effective and safe.⁸ Many chemotherapeutic agents are themselves derived from botanical sources,⁹ and preliminary findings have shown a potentially beneficial effect with some herbal compounds in cancer treatment.¹⁰

The botanical compound LCS101 is comprised of a number of herbal components and was developed based on the principles of Chinese herbal medicine. LCS101 consists of a mixture of varying quantities of dry powdered extracts of the following Chinese medicinal herbs: *Astragalus membranaceus*; *Atractylodes macrocephala*; *Citrus reticulata*; *Glehnia littoralis*; *Ligustrum lucidum*; *Lycium chinense*; *Milletia reticulata*; *Oldenlandia diffusa*; *Ophiopogon japonicus*; *Paeonia lactiflora*; *Paeonia obovata*; *Poriae cocos*; *Prunella vulgaris*; and *Scutellaria barbata*. These herbs are considered to be safe for human consumption, and do not alter the pharmacodynamics of anti-cancer agents.¹¹ The use of LCS101 by breast cancer patients is supported by extensive clinical experience, as well as preliminary published research.^{12,13} A randomized, placebo-controlled, double blinded trial found a significant reduction in chemotherapy-induced hematological toxicities in patients with breast cancer receiving adjunct treatment with LCS101. These patients developed significantly

less severe anemia, leucopenia and neutropenia when compared to controls.¹² While the effects on hematological toxicities have been studied, we were unable to locate any studies examining the effects of the compound on treatment-related symptoms.

The current report presents a case series of 20 patients with locally invasive breast cancer who were treated with LCS101 as adjuvant to conventional chemotherapy regimens. The effects of LCS101 on fatigue, weakness, pain and CINV were examined, as was the impact of this treatment on overall function and QOL.

Case Series: Treatment and Assessment

The botanical compound LCS101 is a capsulated preparation of powder produced from dried herbal extracts imported by Zen Herbs Inc (Tel Aviv, Israel) and manufactured under Good Manufacturing Practice conditions. The herbal components of the formula are tested for batch-to-batch consistency, with a certificate of analysis containing chemical and physical identification. The components undergo high-performance liquid chromatography (HPLC) and inductively-coupled plasma (ICP) spectrometry. All batches are analyzed and certified to be free of heavy metals, microbial contaminants, pesticide residues, or mycotoxins. Following an in-depth interview and examination, component dosages are adjusted in accordance with the principles of Chinese herbal medicine. The final product is a capsule containing 2 grams of dried herbal extract powders, which are taken by patients three times daily (for a total of 6 g/day). Treatment with LCS101 is initiated 2 weeks before treatment and is continued until the end of the chemotherapy regimen.

The files of 20 consecutive patients who presented to the treatment center with a diagnosis of locally invasive breast cancer were examined. All patients had received LCS101, in addition to their conventional chemotherapy regimen. The treatment center is an integrative medical center located in central Israel (Tel Aviv), with practitioners of traditional Chinese medicine who work in conjunction with conventional oncologists. At the end of the combined integrative treatment, patients are asked to voluntarily complete a self-administered questionnaire in which they score the severity of the following eight subjective outcome parameters: fatigue and weakness, pain, nausea and



vomiting, loss of appetite, impairment of general function and QOL (see Appendix). These parameters are each scored using a Likert-like scale ranging from 0 to 4 (0 = not at all; 1 = a little bit; 2 = somewhat; 3 = quite a bit; 4 = very much). The questionnaire was developed for clinical use and was based on the Functional Assessment of Cancer Therapy—General (FACT-G) subscale. The FACT-G is a reliable and validated study tool which examines five aspects of patient wellness: physical, social, emotional and functional, as well as “additional concerns”.¹⁴ Patients are also asked to list any adverse effects which they feel may have been caused by the botanical treatment.

Case Series: Treatment Outcomes

Twenty consecutive patient files were examined. All of the patients were female and diagnosed with locally-advanced breast cancer (Table 1). In addition to chemotherapy, all had undergone surgery with axillary lymph node dissection and radiotherapy. All of the patients were Jewish (70% of Ashkenazi origin), and the mean age at diagnosis was 51.0 years. Three-quarters were married, and only one was a current smoker. A *t*-test examining the change in mean hemoglobin levels found a significant reduction from pre- to post-treatment values (from 12.9 to 11.7 g/dL; *P* = 0.021).

Patient scores for symptom severity and impact on function and quality of life are presented in Table 2. Most respondents (70%) reported that at the end of the combined treatment regimen they suffered from either no or only mild levels of fatigue, with 60% reporting none to mild weakness. The majority (85%) reported none to mildly severe pain, and most (70%) reported none to mildly severe nausea and none to mildly severe levels of vomiting (80%). Loss of appetite was scored as severe by only 15% of respondents. At the end of treatment only 20% reported severely impaired function and 40% severely impaired QOL. No adverse effects were attributed by patients to the use of the botanical compound LCS101. The overwhelming majority of respondents (85%) reported that they believed the compound had provided a significantly beneficial effect, helping to reduce treatment-related symptoms.

Discussion

This report examined the effects of the botanical compound LCS101 on symptom severity, function and

Table 1. Demographic and cancer-related data of patients with breast cancer receiving LCS101 treatment for chemotherapy-related symptoms (n = 20).

Demographic data	
Mean age (range)	52.85 ± 9.22 (30–64)
Ethnic origin	
Jewish (Ashkenazi)	14
Jewish (Sephardic)	6
Marital status	
Single	1
Married	15
Divorced	3
Widowed	1
Smoker	1
Cancer-related data	
Mean age at diagnosis (range)	51.0 ± 9.38 (30–63)
Genetic type	
BRCA (1 or 2)	6
Hormonal type	
ER	12
PR	10
HER2	8
Cancer type	
Invasive ductal carcinoma – IDC (grades 2–3)	16
Invasive lobular carcinoma – ILC	2
Ductal carcinoma in situ (DCIS) + IDC	1
Metastatic	1
Surgical treatment	
Lumpectomy/axillary LN dissection	15
Mastectomy/axillary LN dissection	5
Radiation treatment	20
Chemotherapy protocol	
AC (doxorubicin and cyclophosphamide)	5
AC + T (+taxol)	7
CAF (cyclophosphamide, doxorubicin, 5FU)	5
CEF (cyclophosphamide, epirubicin, 5-FU) + taxotere/taxol	3

QOL in a case series of 20 female patients with locally advanced breast cancer undergoing chemotherapy. These patients had aggressive tumors, 80% of them being grade 2–3 invasive ductal carcinomas. In addition to receiving standard chemotherapy regimens, all of the patients had undergone surgery and radiation therapy, both of which can cause severe symptoms. Scores given by patients to their symptoms were significantly less severe than expected, based on what has been described in the literature.

**Table 2.** Symptom severity in breast cancer patients treated with LCS101 (n = 20).

Following chemotherapy, did you suffer from	Mean score \pm SD	None to mild (n) Score: 0–2	Severe (n) Score: 3 and 4
1. Fatigue	1.95 \pm 1.40	14	6
2. Weakness	1.85 \pm 1.31	12	8
3. Pain	0.85 \pm 1.14	17	3
4. Nausea	1.45 \pm 1.50	14	6
5. Vomiting	1.05 \pm 1.43	16	4
6. Decreased appetite	1.35 \pm 1.14	17	3
7. Impaired function	1.45 \pm 1.19	16	4
8. Impaired quality of life	2.00 \pm 1.30	12	8

Fatigue

Fatigue is one of the most frequent symptoms associated with adult cancer survivors, and for patients with breast cancer it may persist for years, even after the completion of adjuvant therapy.^{15–17} In a US study of 1372 patients with breast cancer, fatigue was reported by 81.7% of respondents.⁶ A Dutch study (n = 430) found that 20% of breast cancer patients report persistent fatigue, without any improvement over a 3-year follow-up period. The strongest predictors of fatigue among these patients were mental health score, hemoglobin levels, joint pain and muscle pain.¹⁷

In the present case series, 70% of patients reported none to mild levels of fatigue and 60% reported none to mild levels of weakness. One possible explanation for these low scores may be related to the fact that LCS101 has been shown to reduce chemotherapy-induced hematological toxicity, including anemia.¹² In the present report, hemoglobin levels had decreased by only 1.6 g/dL following treatment, which is considered as only a mild (Grade 1) adverse event.¹⁸ Nonetheless, the design of the current study did not allow for us to examine the association between fatigue and the decrease in hemoglobin levels.

Pain

Chronic and persistent pain can be serious and debilitating for patients with breast cancer. As many as 60% of these patients report aches and pains by the end of their initial treatment.⁶ Post-mastectomy pain is reported by 43% of patients, and as many as half of patients develop a chronic pain syndrome.¹⁵ Many of the chemotherapy agents in use, such as aromatase inhibitors, are associated with pain syndromes,^{19,20} and neuropathy may develop following surgery or

with the use of the taxane agent paclitaxel (Taxol).^{20–22} Finally, an idiopathic entity termed “cancer breakthrough pain” has been described in association with various treatment regimens for breast cancer.²³

In the present case series patients reported low scores for pain. Many (85%) reported none to mild levels of pain, and the mean pain score was 0.85 (possible range: 0–4). It should be noted that all of the patients had undergone surgery and radiation therapy and were on chemotherapy regimens that included aromatase inhibitors, all of which are frequently complicated by pain syndromes. It is possible that the low pain scores reflected the low scores for fatigue and weakness reported by these patients, or the fact that only half of patients had been treated with paclitaxel (Taxol), the prime cause for treatment-induced neuropathy.²²

Chemotherapy-induced nausea and vomiting (CINV)

Symptoms of CINV are common and extremely distressing for cancer patients, with as many as 3/4 of patients reporting chemotherapy-related emesis.^{5,6,24} The risk for CINV is dependent on a number of factors, such as the anti-cancer agents used during treatment. CINV is more prevalent among female and younger patients, as well as among those with a history of nausea or vomiting.⁵ Current guidelines call for routine pre-treatment with anti-emetic medications before initiating any high-risk treatment regimen. Preventive treatments include corticosteroid agents (eg, dexamethasone) and serotonin-receptor antagonists (eg, ondasterone), as well as newer medications.²⁵ These therapies, however, are of limited benefit, with regimens such as ondasterone and dexamethasone



preventing CINV in 42.5% of cases, a rate which increases to only 50.8% with the addition of the NK1-receptor antagonist aprepitant.²⁶ Anti-emetic agents are also limited by potentially serious toxic effects.²⁵

In the present case series, the scores given for CINV were low, with a mean score of 1.45 for nausea and 1.05 for vomiting (possible range: 0 to 4). Scores for the severity of decreased appetite were also low, with a mean score of 1.35 (possible range: 0 to 4). Only 30% of patients reported severe nausea, and only 20% severe vomiting. It is possible that some of the LCS101 herbal components, such as *scutellaria barbata* (Barbat Skullcap), may have direct anti-emetic effects. Extracts and isolated active components from the *Scutellaria* genus have been shown to have antiinflammatory, antioxidative, anxiolytic and antiviral activity.²⁷ A related herb, *scutellaria baicalensis* (Baikal Skullcap), has also been shown to have anti-nausea and anti-emetic effects in a cisplatin-treated rat model.²⁸

Function and quality of life (QOL)

Following treatment, many women with breast cancer continue to experience a reduction in overall function, with concerns regarding QOL. These concerns include emotional distress, fear that the tumor will recur, and possible difficulties in returning to their roles at home, at work and in society.⁶ Disease and treatment-related symptoms have been found to account for a significant amount of the variability in QOL, suggesting that reducing the symptom burden should have positive effects on QOL.⁶ The symptom found to have the greatest impact on QOL outcome measures is fatigue.^{6,29} Other factors have also been associated with poor physical and emotional well-being, such as muscle stiffness, breast sensitivity, aches and pains, a tendency to take naps, difficulty concentrating, mood and social support and the type of treatment administered.³⁰

In the present case series only 20% of patients reported severe impairment of overall function, compared to 40% who reported severely impaired QOL. The reason for this discrepancy is unclear. It is possible that function is more directly related to symptom severity than QOL, with scores for this measure more reflective of physical, emotional, social, role and cognitive functioning. QOL, on the other hand, is a much more multifaceted measure, reflecting

additional psychological, emotional and environmental influences.^{29,30} It is also possible that the reduction of symptoms had a greater impact on function than on QOL as a result of additional unknown factors.

Safety of LCS101 treatment

None of the patients in the current case series reported any adverse effects due to the botanical treatment. LCS101 is both consistent and free of contaminants, and in a clinical trial of 65 patients with chemotherapy-induced hematological toxicities, the botanical compound was well tolerated.¹² However, we did not examine the effects of LCS101 on the pharmacodynamics of the anti-cancer agents being used by these patients. Many herbal agents can induce phase I cytochrome P450 (CYP) enzymes, potentially altering the activity of CYP-metabolized anticancer drugs.³¹ However, herbal compounds can also stimulate phase II enzymes such as uridine diphosphate glucuronosyltransferase and inhibit drug transporters such as P-glycoprotein (P-gp), breast cancer resistance protein (BRCP) and multi-drug resistance proteins (MRPs).³² These latter effects can increase the bioavailability of drugs, offsetting any increase in CYP-mediated metabolism.¹¹

An example of the gap between expected and actual herb-drug interactions is the LCS101 component *Astragalus membranaceus*. *Astragalus* is a popular herbal medicine among cancer patients, and has been shown to induce the enzyme CYP3A4. Nevertheless, this herbal component does not have any negative effects on the pharmacokinetics of anticancer agents.³² The *Astragalus*-based formula Jinfukang (which also contains the LCS101 components *Ophiopogon japonicus*, *Glehnia littoralis* and *Ligustrum lucidum*) has been shown to have anti-cancer immunomodulatory effects, without altering the pharmacokinetics of the anticancer drug docetaxel.³³ Another herbal formula, PHY906, contains the LCS101 components *Paeonia lactiflora* and *Scutellaria spp.* PHY906 has been shown to reduce irinotecan-induced gastrointestinal activity,³⁴ and when given in conjunction with fluorouracil (5-FU), irinotecan and the irinotecan metabolite SN-38, it does not alter the pharmacokinetics of any of these anticancer agents.^{33–36}

Limitations and future directions

A number of methodological limitations need to be addressed in future research. Case series studies



are observational and retrospective, and therefore do not provide the level of evidence found in randomized-controlled trials. The small size of our sample (20 patients) also prevents making any definite conclusions regarding the true benefits of LCS101 as adjuvant to standard anti-cancer treatment. Nevertheless, case reports and case series can serve as the “first line of evidence ... where everything begins”.³⁷ As such, they can play an important role in the progress of medical science and education.³⁸

In addition to the limitations mentioned above, the sample examined may not be representative of the full patient population. The average age reported for Jewish patients in Israel diagnosed with invasive breast cancer is 58.8 years,³⁶ while in the present case series the mean age at diagnosis was only 51.0 years. The questionnaire used in the integrative medical center was developed for clinical use and not for research, though it is based on the FACT-G tool, a valid and reliable instrument. Finally, the efficacy of treatment was dependent on self-report by patients of subjective outcome measures, as opposed to objective parameters. Nevertheless, the scores given by patients to these subjective parameters were much lower than expected, based on the literature. The only difference between the patients of the present case series and a comparable group of patients was the addition of LCS101 to conventional chemotherapy. When comparing the reported scores for symptom severity and impairment of function and QOL to what has been described in the literature, the results are encouraging.

While efficacy still needs to be proven, the implications of these findings may be significant for both patients as well as society, since reducing the suffering of patients and improving their function and QOL can reduce costs and enable more aggressive anti-cancer regimens, which are currently limited by treatment-induced toxicities. The findings of this study should serve as an impetus for further research, inasmuch as the effects of LCS101 on clinical outcomes in breast cancer patients undergoing chemotherapy still need to be tested within the framework of large randomized, controlled clinical trials.

Acknowledgements

We are grateful to Esther Eshkol for her editorial assistance.

Funding

Author(s) disclose no funding sources.

Competing Interests

YM is a shareholder in LifeBiotics Ltd. Other authors disclose no competing interests.

Author Contributions

Conceived and designed the experiments: NS, YM. Analyzed the data: NS, RYZ. Wrote the first draft of the manuscript: NS, YM, RYZ. Contributed to the writing of the manuscript: NS, YM, RYZ. Agree with manuscript results and conclusions: NS, YM, RYZ. Jointly developed the structure and arguments for the paper: NS, YM, RYZ. Made critical revisions and approved final version: NS, YM, RYZ. All authors reviewed and approved of the final manuscript.

Disclosures and Ethics

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Appendix 1. Questionnaire used to evaluate treatment-related symptoms.

	Not at all	A little bit	Some-what	Quite a bit	Very much
1. Did you feel tired during chemotherapy?	0	1	2	3	4
2. Did you feel weak during chemotherapy?	0	1	2	3	4
3. Did you suffer from any pain during chemotherapy?	0	1	2	3	4
4. Did you suffer from nausea during chemotherapy?	0	1	2	3	4
5. Did you suffer from vomiting during chemotherapy?	0	1	2	3	4
6. Was your appetite decreased during chemotherapy?	0	1	2	3	4
7. Was your level of function impaired during chemotherapy?	0	1	2	3	4
8. Was your quality of life reduced during chemotherapy?	0	1	2	3	4
9. Do you think the herbal medicine helped during chemotherapy?	0	1	2	3	4