A Prospective, Controlled Study of the Botanical Compound Mixture LCS101 for Chemotherapy-Induced Hematological Complications in Breast Cancer

NEORA YAAL-HAHOSHEN,^a YAIR MAIMON,^{b,e} NAVA SIEGELMANN-DANIELI,^d SHAHAR LEV-ARI,^b
ILAN G. RON,^a FANI SPERBER,^c NOAH SAMUELS,^f JACOB SHOHAM,^g OFER MERIMSKY^a

^aDepartment of Oncology, Tel Aviv Sourasky Medical Center affiliated with the Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel; ^bUnit of Complementary Medicine and ^cBreast Imaging Unit, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel; ^dMaccabi Healthcare Services, Tel Aviv, Israel; ^eRefuot Integrative Medical Center, Tel Aviv, Israel; ^fCenter for Integrative Complementary Medicine, Shaare Zedek Medical Center, Jerusalem, Israel; ^gFaculty of Life Sciences, Bar-Ilan University, Ramat Gan, Israel

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ABSTRACT

Background. This prospective, controlled study evaluated the safety, tolerability, and efficacy of the mixture of botanical compounds known as LCS101 in preventing chemotherapy-induced hematological toxicity in breast cancer patients.

Methods. Female patients diagnosed with localized breast cancer were randomly allocated to receive treatment with either LCS101 or placebo capsules, in addition to conventional chemotherapy. The study intervention was initiated 2 weeks prior to the initiation of chemotherapy and continued until chemotherapy was completed, with participants receiving 2 g of LCS101 capsules thrice daily. Subjects were assessed for the development of hematological and nonhematological toxicities, as well as the tolerability and safety of the study intervention.

Results. Sixty-five breast cancer patients were recruited, with 34 allocated to LCS101 and 31 allocated to

placebo treatment. Patients in the treatment group developed significantly less severe (grades 2–4) anemia ($p < .01$) and leukopenia ($p < .03$) when comparing grades 0–1 with grades 2–4, with significantly less neutropenia ($p < .04$) when comparing grades 0–2 with grades 3–4. This effect was more significant among patients undergoing a dose-dense regimen. No statistically significant effect was found with respect to nonhematological toxicities, and side effect rates were not significantly different between the groups, with no severe or life-threatening events observed in either group.

Conclusion. The addition of LCS101 to anthracycline- and taxane-based chemotherapy is safe and well tolerated, and may significantly prevent some chemotherapy-induced hematological toxicities in early breast cancer patients. These results should encourage further larger and more extensive clinical trials. *The Oncologist* 2011;16:1197–1202

Correspondence: Yair Maimon, Ph.D., Refuot Integrative Medical Center, 18 Feinstein Street, Tel Aviv 69123, Israel. Telephone: 972-3-744-0888; Fax: 972-3-677-7768; e-mail: yair@tcm.org.il Received April 28, 2011; accepted for publication May 19, 2011; first published online in *The Oncologist Express* on June 28, 2011. ©AlphaMed Press 1083-7159/2011/\$30.00/0 <http://dx.doi.org/10.1634/theoncologist.2011-0150>

INTRODUCTION

Breast cancer is currently the most prevalent female malignancy worldwide (one in eight women will be diagnosed with this disease during their lifetime), and it is a significant cause of morbidity and mortality [1]. Although the majority of patients are diagnosed with localized tumors, more than half will be exposed to chemotherapy at some time during the course of their disease, usually with regimens that combine anthracyclines and taxanes [2]. The addition of other chemotherapy drugs to an established regimen increases tumor response, although this positive effect is offset by greater toxicity [3].

Hematological complications of chemotherapy are common, and may delay or require dose reduction in planned chemotherapy [4, 5], as well as significantly affecting patient quality of life [6, 7]. The current treatment of chemotherapy-induced hematological toxicities is geared toward correcting the blood count, and is not itself without side effects and expense. Transfusion is the main treatment for chemotherapy-induced anemia, and erythropoietin-stimulating agents are limited by potentially toxic effects [8]. Chemotherapy-induced neutropenia is treated with G-CSF, which though relatively safe is also not without side effects, and the economic evidence for its use in the prophylactic treatment of febrile neutropenia in early-stage breast cancer patients is limited [9]. Finally, most thrombopoietic agents are still under investigation, and some (such as interleukin-11) are of limited use because of their narrow therapeutic index [10].

Many patients diagnosed with breast cancer turn to complementary and alternative medicine [11], with herbal medicine being one of the most popular modalities [12, 13]. In Europe, nearly half of breast cancer patients report using botanical medicines [14], and in China, 86.4% are using Chinese herbal medicine (CHM), in addition to conventional treatment [15]. A systematic review (including seven randomized controlled trials with 542 subjects) concluded that CHM, when used in conjunction with chemotherapy, may improve bone marrow and quality of life, though the evidence is too limited to make any confident conclusions [16]. Similar conclusions have been reported with colorectal cancer [17] and non-small cell lung cancer [18] as well. A clinical trial evaluating patients with early-stage breast and colon cancer ($n = 120$) did not find a lower incidence of postchemotherapy hematological toxicity in those treated with CHM, although a significant impact in the control of nausea was found [19].

LSC101 is a homogeneous mixture of dry powdered extracts of botanical compounds from the following herbs: *Astragalus membranaceus*, *Poriae cocos*, *Atractylodes macrocephala*, *Lycium chinense*, *Ligustrum lucidum*,

Paeonia lactiflora, *Paeonia obovata*, *Citrus reticulata*, *Ophiopogon japonicus*, *Milletia reticulata*, *Oldenlandia diffusa*, *Scutellaria barbata*, *Prunella vulgaris*, and *Glehnia littoralis*. These herbs are all considered to be safe for human consumption, and the mixture was developed in accordance with principles of CHM, supported by extensive clinical experience. In a mouse breast cancer model, the addition of these botanical compounds to doxorubicin led to significantly better peripheral neutrophil counts, and preserved splenic erythrocyte and leukocyte counts (unpublished data). The current study evaluated the ability of LCS101 to prevent hematological toxicity—as reflected by the severity of the toxicities (according to grade) anemia, leukopenia, and thrombocytopenia—in women with breast cancer undergoing chemotherapy. The ability to prevent nonhematological toxicities as well as the safety and tolerability of the compounds were examined as well.

PATIENTS AND METHODS

Patient Selection

Patients were treated at the Tel Aviv Sourasky Medical Center (Tel Aviv, Israel), a national oncological referral and research center (<http://www.tasmc.org.il/sites/en/Pages/default.aspx>). Patients aged 18–69 years with newly diagnosed, nonmetastatic, and histologically proven carcinoma of the breast who were scheduled to receive anthracycline-based regimens (with or without taxanes) were eligible. Patients with a Karnofsky performance status score <80%, a history of chemotherapy or second malignancy (other than cervical carcinoma in situ or nonmelanoma skin tumors) within the last 5 years, impaired hepatic or renal function (more than two times the upper normal range), or blood counts with a hemoglobin level <10 g/dL, WBC < 3,000, or platelet count < 100,000 were excluded.

The sample size for this pilot study was determined using SAS/STAT software (SAS Institute, Inc., Cary, NC) on the basis of the calculation that 50% of patients would develop toxicity (Common Toxicity Criteria, Version 2 [CTC-V2] grade ≥ 2) [20] from adjuvant chemotherapy. Although this is the first clinical trial evaluating the study drug, clinical experience indicated an expected 25% lower rate of hematological toxicities in treated patients. As such, 60 study patients (30 in each group, with an additional 10% for anticipated dropouts) were calculated to be needed in order to detect a similar difference in a single toxicity using a two-sided χ^2 test with a power of 80% at a significance level <.05. All patients provided written informed consent before any study procedures were performed. The study was approved by the investigational review board at the participating medical center, and was conducted in accor-

dance with the ethical principles of the Declaration of Helsinki and in compliance with good clinical practice and national regulatory guidelines.

Study Design and Treatments

The study was a single-center, randomized, double-blinded trial comparing LCS101 treatment with placebo. All patients, physicians, and attending staff were blinded to treatment group assignment. Chemotherapy regimens were determined at the discretion of the attending physician, and included the following regimens: (a) doxorubicin (60 mg/m²) and cyclophosphamide (600 mg/m²) every 3 weeks, for a total of four cycles (AC regimen); (b) the AC regimen followed by weekly paclitaxel (80 mg/m² per week) for 12 cycles or docetaxel (36 mg/m² per week) for 12 cycles as well; (c) dose-dense AC every 2 weeks for four cycles followed by paclitaxel (175 mg/m²) for four cycles every 2 weeks, supported with the neutrophil stimulants filgrastim or pegfilgrastim. Patients receiving regimen (a) or (b) could receive epirubicin (90 mg/m²) instead of AC at the discretion of the attending physician. No delay in any of the above treatment regimens occurred as a result of participation in the study.

Each LCS101 capsule contained 0.4 g of the botanical mixture, with extracts manufactured according to good manufacturing practice conditions and imported under license (Zen Herbs Inc., Tel Aviv, Israel), in accordance with the regulations of the Israel Ministry of Health. The capsules were tested for batch-to-batch consistency, with a certificate of analysis containing chemical and physical identification as well as undergoing high-performance liquid chromatography and inductively coupled plasma spectrometry. All batches were analyzed and certified to be free from heavy metals, microbial contamination, pesticide residues, and mycotoxins. The placebo capsules consisted of bread crumbs (0.4 g as well) and were provided by the same company. Placebo medication resembled the LCS101 capsules in texture, appearance, smell, and taste.

Following enrollment, patients were randomly allocated to receive either true (LCS101) or placebo capsules, with an allocation ratio of 1:1, in addition to the conventional chemotherapy regimen. Simple randomization was implemented using the Random Allocation Software program [21]. Treatment with the study medication was initiated 2 weeks prior to the first dose of chemotherapy and continued throughout the chemotherapy treatment or until the patient was lost to follow-up. Each patient received a sealed container with a 21-day supply of 315 capsules, that is, five capsules per day to be taken 30 minutes before meals three times daily (6 g/day). In order to establish adherence to the study protocol, patients were asked to return the con-

tainers every 3 weeks so that the study coordinator could count the number of remaining capsules, after which they were provided with a new package with their next 21-day supply.

Assessment

Follow-up visits were conducted by the attending physician prior to each chemotherapy cycle and entailed a complete history, physical examination, and blood counts. During some of these visits, and at the discretion of the attending physician, blood biochemistry was performed as well. All laboratory tests were conducted in the clinical laboratories of the study center.

The study primary endpoint was a reduction in hematological parameters, as measured by a CBC with differential. The severity of chemotherapy-induced hematological toxicity was graded according to the National Cancer Institute CTC-V2 [20]. Secondary endpoints for assessment were nonhematological chemotherapy-induced toxicities, which were also graded according to the CTC-V2. The safety of the study treatment was evaluated according to self-reporting of adverse events, as recorded in hospital patient records.

All randomized patients were included in the intention-to-treat analysis. The intervention and placebo groups were compared using *t*-tests for continuous parameters and χ^2 tests (of Fisher's exact test) for categorical variables. SAS for Windows (version 9.1.3) was used for all statistical analyses.

RESULTS

From January 2005 to December 2007, 65 patients were screened and treated. Of these, 34 were randomly allocated to the LCS101 treatment group and 31 were randomly allocated to the placebo treatment group. Two patients from each study group withdrew their participation after consent and randomization, with all randomized patients included for analysis. The characteristics of the study group, histology, and chemotherapy regimens are outlined in Table 1.

Treatment Exposure

Patients received chemotherapy in both the adjuvant (75.3%) and neoadjuvant (27.7%) settings, with dose-dense and taxane-based regimens distributed equally between the two groups. Complete adherence to the treatment protocol was observed in 24 of 34 patients in the LCS101 treatment group, with an additional five completing >50% of the protocol. In the placebo group, 17 of 31 patients completed the study protocol in its entirety, with seven participating in >50%. In the LCS101 group, seven patients discontinued study treatment because of difficulty swallowing the nu-

Table 1. Patient demographics			
Characteristic	LCS101 ^a	Placebo	<i>p</i> -value
<i>n</i> of patients	34	31	
Median age (range), yrs	47.6 (24–67)	52.2 (28–68)	.17
Karnofsky performance status score			
100%	27 (79%)	25 (81%)	
90%	3 (9%)	4 (13%)	
80%	4 (12%)	2 (6%)	
Histology			
Invasive ductal carcinoma	21	24	.32
Invasive lobular carcinoma	2	2	
Invasive ductal and lobular carcinoma	11	5	
Estrogen receptor positive	26	26	.46
HER-2 positive	3	9	.11
Chemotherapy			
Neoadjuvant	9	9	
Adjuvant	25	22	
Dose dense	9	9	
AC every 3 wks	25	22	

^aLCS101 is a mixture of several botanical compounds. See text for details.
Abbreviations: AC, doxorubicin and cyclophosphamide; HER-2, human epidermal growth factor receptor 2.

merous capsules, with another patient stopping treatment after developing abdominal pain and nausea. In the placebo group, eight discontinued treatment because of difficulty in swallowing the capsules and four more discontinued because of abdominal pain or nausea. No severe or life-threatening events were reported in either group.

Efficacy

Hematological toxicities (grades 0–1 and 2–4) following chemotherapy in the two treatment arms are outlined in Table 2. There were significantly fewer patients in the LCS101 group who developed severe anemia and leukopenia than in the placebo group. There was also a trend in favor of the LCS101 group with respect to a lower incidence of neutropenia, and when comparing grades 0–2 with grades 3–4 this trend became significant ($p = .04$). When each severity grade was evaluated separately, there was a significant benefit observed in the LCS101 group with respect to the development of grade 1 anemia ($p < .01$), grade 2 leukopenia ($p < .05$), and grade 2 neutropenia ($p < .05$).

Table 2. Hematologic toxicity according to treatment arm			
Toxicity	<i>n</i> of patients (%)		<i>p</i> -value
	Grade 0–1	Grade 2–4	
Anemia			
LCS101	28 (82)	6 (18)	
Placebo	16 (52)	15 (48)	<.01
Leukopenia			
LCS101	28 (82)	6 (18)	
Placebo	18 (58)	13 (42)	.03
Neutropenia			
LCS101	25 (74)	9 (26)	
Placebo	16 (52)	15 (48)	.06
Lymphopenia			
LCS101	23 (68)	11 (32)	
Placebo	16 (51)	15 (49)	.21
Thrombocytopenia			
LCS101	34 (100)	0	
Placebo	28 (30)	2 (70)	.21

Among those patients undergoing the dose-dense regimen (every 3 weeks), LCS101 treatment showed an even greater protective effect, with only 4% of patients developing grade 2 anemia, as opposed to 50% of patients receiving placebo treatment ($p < .01$). None of these patients treated with LCS101 developed grade 2 neutropenia, compared with 33% of the placebo group, although this trend was not statistically significant ($p = .06$). No significant differences were found between groups with respect to the development of thrombocytopenia (though there were too few patients with grades 2–4 thrombocytopenia) or febrile neutropenia, which occurred in two of the LCS101 patients and four of the placebo patients ($p = .32$). Nor were there any differences observed between the groups with respect to any of the nonhematological toxicities examined (Table 3).

DISCUSSION

Chemotherapy-induced hematologic toxicities are a common and significant complication with the treatment of breast cancer, limiting both the frequency and intensity of treatment protocols. Current conventional treatment is geared toward treating the outcomes of this toxicity, and not prevention, and is limited by significant side effects and expense. This pilot study demonstrated that the addition of the botanical compound mixture LCS101 to conventional chemotherapy regimens is both safe and feasible in patients

Table 3. Nonhematologic toxicity according to treatment arm			
Symptom	Grade 0–1	Grade 2–4	p-value
Musculoskeletal pain			
LCS101	32	2	
Placebo	31	0	.49
Constipation			
LCS101	33	1	
Placebo	30	1	1.0
Fatigue			
LCS101	31	3	
Placebo	25	6	.48
Flushing			
LCS101	34	0	
Placebo	28	3	.24
Infection			
LCS101	34	0	
Placebo	28	3	.24
Nausea			
LCS101	28	6	
Placebo	24	7	.76
Neutropenic fever			
LCS101	32	2	
Placebo	27	4	.32
Pain			
LCS101	32	2	
Placebo	30	1	1.0
Peripheral neuropathies			
LCS101	27	7	
Placebo	26	5	.75
Vomiting			
LCS101	30	4	
Placebo	30	1	.35

with early breast cancer, and it appears to provide protection against mild to moderate chemotherapy-induced anemia and neutropenia, but not thrombocytopenia.

It is not clear how the botanical compounds in LCS101 reduce hematological toxicity. Some of the herbs, such as *Ophiopogon japonicus*, have been shown to stimulate production of erythroid progenitor cells in mice [22], whereas *Astragalus membranaceus* has been shown to promote recovery of hematopoietic function in patients with chronic aplastic anemia [23], although the implications of these activities for chemotherapy-induced hematological toxicity

are still not clear. CHM emphasizes the importance of using compounds that integrate the properties of various botanicals. However, the true nature of the interactions among the botanical components is also unclear. The study sample size was small, and the low concentration of the compounds meant that participants needed to ingest a large number of capsules. Increasing the concentration of these components in future studies will allow for a reduction in dosing, increasing adherence to the protocol and reducing the dropout rate. Future large studies will need to examine the effects of LCS101 with more uniform chemotherapy regimens, giving a clearer picture as to the protocols that benefit most from the addition of the botanical compounds. Other outcome measures, such as overall survival, progression-free survival, and quality-of-life parameters, need to be addressed in future studies, as well as the interactions between the herbal components of the study drug and chemotherapy agents.

The results of this trial encourage additional study, within a framework of larger and more extensive clinical trials. The reduction in chemotherapy-induced hematological toxicities is of significant importance, both with respect to the need for postchemotherapy treatment and hospitalization and for completing treatment regimens and enabling the use of higher doses of chemotherapy.

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Neora Yaal-Hahoshen and Yair Maimon contributed equally to this work.

AUTHOR CONTRIBUTIONS

Conception/Design: Neora Yaal-Hahoshen, Yair Maimon, Noah Samuels, Nava Siegelmann-Danieli, Shahar Lev-Ari, Ilan Ron, Fani Sperber, Jacob Shoham, Ofer Merimsky

Provision of study material or patients: Neora Yaal-Hahoshen, Nava Siegelmann-Danieli, Ilan Ron, Ofer Merimsky

Collection and/or assembly of data: Neora Yaal-Hahoshen, Yair Maimon, Noah Samuels, Nava Siegelmann-Danieli

Data analysis and interpretation: Neora Yaal-Hahoshen, Yair Maimon, Nava Siegelmann-Danieli, Shahar Lev-Ari, Noah Samuels, Fani Sperber, Jacob Shoham, Ofer Merimsky

Manuscript writing: Neora Yaal-Hahoshen, Yair Maimon, Nava Siegelmann-Danieli, Noah Samuels, Shahar Lev-Ari

Final approval of manuscript: Yair Maimon, Nava Siegelmann-Danieli, Shahar Lev-Ari, Ilan Ron, Fani Sperber, Noah Samuels, Jacob Shoham, Ofer Merimsky

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