Letter to the Editor Regarding “A Prospective, Controlled Study of the Botanical Compound Mixture LCS101 for Chemotherapy-Induced Hematological Complications in Breast Cancer” by Yaal-Hahoshen et al. (*The Oncologist* 2011;16:1197–1202)

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Disclosures: Jan H.M. Schellens: Lilly (C/A). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

Based on the results of a prospective, randomized, placebo-controlled study of Yaal-Hahoshen et al., [1] the authors concluded that the botanical mixture LCS101 prevented hematological complications in breast cancer patients undergoing anthracycline- and taxane-based chemotherapy. They also concluded that the addition of LCS101 to conventional chemotherapy regimens “is both safe and feasible in patients with early breast cancer, . . .”. However, we believe that these conclusions should be interpreted with caution because the present study has a few major limitations.

First, the possible pharmacodynamic (PD) effect of LCS101 on the bone marrow was not evaluated directly in the present study. Yaal-Hahoshen et al. [1] primarily determined hematological parameters by counting erythrocytes, leukocytes, neutrophils, lymphocytes, and thrombocytes in the peripheral blood. These parameters only secondarily reflect bone marrow function. It would be more accurate to evaluate the growth of progenitor cells such as colony-forming unit (CFU)-granulocytes, erythroids, macrophages and megakaryocytes; burst-forming units-erythroids; and CFU-granulocyte-macrophages [2].

Currently, the effect of LCS101 on hematopoietic function

has barely been investigated. The authors only reported that the “addition of LCS101 to doxorubicin led to significantly better peripheral neutrophil counts, and preserved splenic erythrocyte and leukocyte counts” in a mouse breast cancer model. Unfortunately, these data were not published.

For a few individual LCS101 components, however, a PD effect on bone marrow function could be expected. For example, the production of erythroid progenitor cells has been stimulated by *Ophiopogon japonicus* in mice [3], and in patients with chronic aplastic anemia hematopoietic recovery has been promoted by *Astragalus membranaceus* [4]. As Yaal-Hahoshen et al. [1] reported, it is still unclear what the implications of these activities are for chemotherapy-induced hematological toxicity. Additionally, it is unknown whether the components may interact synergistically or additively with each other, which complicates predicting the effect of LCS101 on hematopoietic function.

Second, in the present study no pharmacokinetic (PK) analysis of the administered anticancer drugs (such as doxorubicin, paclitaxel, and docetaxel) was performed. Therefore, it is not possible to exclude possible PK interactions between LCS101 and these anticancer drugs. Regarding the effects of LCS101 on the

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PK of anticancer drugs, there is no information available because no PK interaction studies with LCS101 have been performed.

However, based on in vitro results with individual LCS101 components, PK interactions between LCS101 and anticancer drugs metabolized by cytochrome P450 (CYP)3A4 cannot be ruled out. Using a reporter gene assay and real-time polymerase chain reaction, six LCS101 components induced pregnane X receptor (PXR)-regulated CYP3A4 transcription in HepG2 cells: *Astragalus membranaceus*, *Poriae cocos*, *Atractylodes macrocephala*, *Lycium chinense*, *Ophiopogon japonicus*, and *Paeonia lactiflora* [5]. Furthermore, according to our preliminary results based on a reporter gene assay, the LCS101 compound *Oldenlandia diffusa* is also a potent inducer of PXR-regulated CYP3A4 transcription in LS180 cells (unpublished data). Thus, because CYP3A4 is involved in the metabolism of doxorubicin [6], docetaxel [7], and paclitaxel [8], CYP3A4 induction might lead to lower systemic exposure of these anticancer drugs and consequently to the reported lower incidence of hematological toxicities in cancer patients who received LCS101. Therefore, it is important to evaluate the potential PK interactions between LCS101 and anticancer drugs in clinical PK studies.

Third, the PD effect of LCS101 on the tumor, and thus the efficacy of the administered anticancer drugs, was not evaluated. The statement from Yaal-Hahoshen et al. [1] that the addition of LCS101 to conventional chemotherapy is safe and feasible implies that the antitumor effect of chemotherapy is not negatively affected by LCS101. However, their study did not evaluate the possible PD effects of LCS101 on the tumor. This would have provided valuable information because there currently are no clinical data regarding the effects of LCS101 on the antitumor effect of the administered anticancer drugs. It has only been shown for one individual LCS101 component (*Ligustrum lucidum*) that doxorubicin-induced apoptosis was enhanced in human colorectal carcinoma DLD-I cells [9]. De-

termination of the PD effects of LCS101 on the tumor could have been assessed by tumor size evaluation using the Response Evaluation Criteria in Solid Tumors. In the present study, however, the sample size was too small to exclude a PD effect of LCS101 on the tumor. To assess the PD effect of LCS101 on the tumor during neoadjuvant chemotherapy using a noninferior study design, ~1,200 patients would be required based on a significance level of 0.05, probability (power) of 0.80, noninferiority margin of 5%, and overall clinical response rate of 86% for chemotherapy with doxorubicin plus cyclophosphamide [10]. This is a substantially larger number of patients than the 18 patients who underwent neoadjuvant chemotherapy in the present study.

In conclusion, Yaal-Hahoshen et al. [1] claimed that the addition of LCS101 to conventional chemotherapy is safe and feasible in patients with early breast cancer. However, their study lacks essential information regarding the hematoprotective mechanism of action of LCS101, potential PK interactions with chemotherapy, and the PD effects of LCS101 on the tumor. Therefore, we recommend the execution of PK interaction studies with LCS101 and anticancer drugs. In addition, the PD effects of LCS101 on hematopoietic function and on tumors should also be evaluated clinically. Until these studies have been executed, we advise not to combine LCS101 with anticancer drugs.

ACKNOWLEDGMENT

Kim D. Mooiman and Andrew K.L. Goey contributed equally to this work and should be considered as first authors.

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