

Regulatory T-cell modulation by green tea in Chronic Lymphocytic Leukemia

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Regulatory T cells (Tregs) are a small subset of CD4⁺ T lymphocytes that is thought to play a key role in modulation of the immune response. These cells are involved in the development and in the control of many autoimmune conditions and in the control of immune responses towards transformed cells. Tregs have been associated to cancer development and progression, in many types of cancer, including CLL in which their number is found increased in peripheral blood (Giannopoulos et al., 2008; D'Arena et al., 2011 and 2012). Rai stage 0 identifies patients with early stage CLL for which there is no effective intervention at the present time and a 'wait and see' policy is usually adopted.

Green tea is a popular beverage in China and Japan and is becoming increasingly popular in Western countries due to its beneficial effects. Some biological and clinical studies have reported that green tea constituents, such as epigallocatechin-gallate (EGCG), have antitumor effects on hematologic malignancies including CLL (Shanafelt et al., 2009).

We report data on a clinical trial in which green tea extracts were given orally to 12 patients with stage 0 CLL and 12 healthy subjects. Aim of our study was to evaluate if green tea consumption is able to modulate circulating Tregs and peripheral blood neoplastic B-cells. We used a combination of CD4/CD25/CD127 to evaluate, by flow cytometry, the number of circulating Treg cells. A commercially available enzyme-linked immunosorbent assay (ELISA) was used to assay for IL-10 and transforming growth factor (TGF)- β into plasma samples.

Ten patients and 10 controls completed the 6-month scheduled therapy. Two patients and 2 controls stopped therapy within 1 month because of tachycardia and epigastralgia. Eight out 10 evaluable patients (80%) showed a reduction of lymphocytosis and absolute number of circulating Tregs, as well. One patient (10%) had a stabilization of lymphocytosis and a reduction of Tregs, and 1 patient (10%) showed an increase of both lymphocytosis and Tregs. Only the non-responding patient progressed after 5 months from the end of green tea administration and chemotherapy was given.

The observed reduction of circulating Tregs suggests a modulation of immune system regulation by a green tea component, such as EGCG. This is further confirmed by the observation that both IL-10 and TGF- β serum concentrations decreased as effect of green tea intake.

Our assumption was that Tregs reduction could be induced by oral green tea and that this modification could impact on clinical and biological features of the disease. In fact, in patients in whom Tregs have reduced their number, a decrease in lymphocytosis was also observed. If Tregs are actors or just innocent bystanders of immunological phenomena far more complex and not yet fully understood has to be clarified with more and better targeted *in vitro* studies. Taken together, these data strongly encourage the use of green tea at a given point of clinical course and follow-up of patients with CLL. In fact, oral green tea is a well-tolerated and 'pleasant' tool that could be useful to prolong the early stage phase of CLL disease and to prolong the remission phase after therapy in progressed patients underwent disease specific treatment (O'Brien et al., 2011). On the other hand, the use of non-conventional medicines, especially herbal remedies, other than green tea, is common in cancer patients, including hematological neoplasias (Ben-Arye et al., 2010). The oncology community must be aware of this unconventional approach, adequately advise their patients, warning them of potential side effects, contraindication and risks.

Giannopoulos et al. (2008) *Oncol Rep.* 20:677-82.

D'Arena et al. (2011) *Leuk Res.* 35:363-68.

D'Arena et al. (2012) *Am J Hematol.* 87:628-31.

Shanafelt et al. (2009) *J Clin Oncol.* 27:3808-14.

O'Brien et al. (2011) *Clin Adv Res Hematol Oncol.* 9:22-1.

Ben-Arye et al. (2010) *Leuk Lymphoma.* 51(8):1414-23.