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Curcumin and EGCG Suppress Apurinic/Apyrimidinic Endonuclease 1 and Induce Complete Remission in B-cell Non-Hodgkin's lymphoma Patients

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ABSTRACT:

Background: Follicular lymphoma (FL) is the most common subtype of indolent lymphoma. FL is still considered to be an incurable disease and palliation of symptoms is an acceptable approach to the expected pattern of repeated relapses due to developing resistance to chemotherapy agents. Apurinic/apyrimidinic endonuclease/redox factor-1 (APE1/Ref-1) is a multifunctional protein involved in DNA base excision repair (BER) of oxidative DNA damage and in redox regulation of a number of transcription factors. It was observed that cytoplasmic APE1 induced COX-2 expression through NF-κB activation. It has been shown that chemopreventive agents potentiate the efficacy of chemotherapy through the regulation of multiple signaling pathways, including NF-κB, c-Myc, cyclooxygenase-2, apoptosis, and others, suggesting a multitargeted nature of chemopreventive agents. We hypothesized that curcumin, a polyphenolic antioxidant derived from the spice turmeric, and epigallocatechin gallate (EGCG) from green tea would potentiate the effect of chemotherapy in B-cell lymphoma.

Objective: We examined the role of human apurinic/apyrimidinic endonuclease 1 (APE1) in resistance and prognosis in patients with FL. Our major objective was to update the safety and efficacy results of the antitumor effect of combination of curcumin and EGCG therapy in relapsed or resistant indolent or transformed non-Hodgkin follicular lymphoma patients and their peripheral blood mononuclear cells (PBMCs) compared with healthy donors' controls.

Methods: Thirty patients with FL with over-expression of constitutive active NF-κB in their PBMCs received regular CHOP and consumed capsules compatible with curcumin doses between 0.9 and 5.4 g daily for up to 9 months and 9.0 g/day green tea whole extract "1000 mg tablets of green tea whole extract containing 200 mg EGCG. We designed a dose-escalation

study to explore the efficacy of CHOP in combination with curcumin and the green tea extract epigallocatechin-3 gallate (EGCG) on the viability of patients' peripheral blood mononuclear cells (PBMCs) lymphocytes.

Results: Treatment of patients with the combination of curcumin and EGCG, significantly lower cytoplasmic APE1 and the levels of the transcription factor were lower than those predicted from the effects of the CHOP agents (cyclophosphamide, doxorubicin, vincristine, and prednisone) alone, especially with a blunting of the remarkable increases in NF- κB activation induced by CHOP. Eighteen of the patients had a CR (18/30), and twelve patients had PR (12/30) within 9 month treatment and followed up to 12 months. They remain disease-free a mean of 8.6 y (range, 7.9–9.2 y) after this combination therapy.

Conclusion: Optimal patient benefit might be obtained in follicular lymphoma when administering curcumin up-front in combination with chemotherapy and EGCG treatment. The combination of curcumin with EGCG resulted in a synergistic antitumor activity and that with CHOP agents in additivity or sub-additivity, down-regulated the expression of all NF-κB regulated gene products, leading to the suppression of angiogenesis, metastasis and entering in complete remission as indicated by β2-microglobulin and lactate dehydrogenase (LDH) levels.

Key words: Curcumin, EGCG, B- cell NHL, NF-κB, VEGF, APE1, lymphoma