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The Future of Breast Cancer Treatment Relies on Getting in Touch with Mother Nature and Stepping Back on the TRAIL

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Editorial

Breast cancer is one of the most overwhelming and deadly forms of cancer affecting women worldwide. The traditional way to treat breast cancer today is "cut, poison, and burn" which relates to surgery, chemotherapy, and radiation respectively [1,2]. While surgery has a direct and obvious effect in removing the majority of the tumor, chemotherapy (with drugs which are mostly alkylating agents deriving from nerve gas) and radiation therapies are based on the principle of damaging the DNA of the cancer cells in order to induce the intrinsic pathway of apoptosis [3]. Thus, chemotherapy with alkylating agents and radiation treatments depend directly on the integrity of p53 which is the inducer of the intrinsic pathway of apoptosis. However, many breast cancers possess a mutated non-functional p53 gene or some breast cancer cell lines proceed with ubiquitination of p53, which in turn is destroyed by the proteasome [3,4]. In both cases, the net result is a defective/absent p53 and chemotherapy and radiation regularly results in necrosis rather than apoptosis of the tumor. The overwhelming amount of cellular debris resulting from necrosis is toxic for the organism. It is also noteworthy that normal non-cancerous cells and tissues surrounding the tumor or tissues that multiply rapidly (i.e. immune tissue, digestive tissue, and epithelial tissue) possess a normal p53 gene and protein and absorb some of the radiation and a substantial amount of the chemotherapy drugs. As a consequence, these normal cells undergo regular apoptosis resulting in the known adverse side effects observed in all patients treated by these methods [5].

Human tumor necrosis factor-related apoptosis-inducing ligand (hTRAIL) is a cytokine that possesses the capability to induce both pathways of apoptosis (extrinsic at first and intrinsic subsequently) in cancer cells while it does not harm normal, non-transformed cells [6,7]. However, one pitfall observed throughout the years *in vitro* and in a multitude of human trials *in vivo* is the resistance of cancer cell lines to hTRAIL-induced apoptosis [8-11]. Several hypotheses for the resistance to TRAIL have been advanced but the most plausible are diminished expression of death receptors (DRs) 4 and 5 for TRAIL on the surface of cancer cells and/or increased expression of inhibitors of apoptosis [7]. Cancer cells with these phenotypes are usually resistant to hTRAIL.

We have used an optimized cDNA to generate high concentrations of a non-tagged version of the soluble portion of recombinant human tumor necrosis factor-related apoptosis-inducing ligand (rhTRAIL). We have shown that this recombinant molecule together with several natural compounds are efficient in inducing apoptosis in previously described breast cancer TRAIL-resistant cell lines. We have proposed the application of "mother-nature"-derived compounds quercetin and silibinin as sensitizing agents to deter rhTRAIL resistance in these cell lines [12,13]. Through our investigations, we determined that quercetin and silibinin were effective sensitizing agents and augmented rhTRAIL-induced apoptosis in rhTRAIL-resistant breast carcinoma especially the more fatal triple negative breast cancer [12,13]. Quercetin and silibinin boosted the expression of DR5 transcriptionally, while silibinin also increased the expression of DR4 transcriptionally [12,13]. Additionally, quercetin and silibinin decreased the expression of anti-apoptotic proteins. Quercetin enhanced the ubiquitination of the anti-apoptotic protein c-FLIPL aiding its proteasome-mediated degradation [13]. Silibinin transcriptionally down-regulated the anti-apoptotic protein survivin [12]. These combined results suggest an efficacious way of treating breast cancer patients in the future. We propose the following protocol: 1) patients should be treated with high concentrations of quercetin and silibinin for five to ten days; 2) in a second step patients should be immediately

treated with rhTRAIL infusions at a maximum dose of 100mg/kg as previously described [9-11,14,15]. Under this protocol, and using natural non-harmful substances, and rhTRAIL that is already approved for human trials cancer patients are "primed" to accept the rhTRAIL which under the conditions described will only destroy cancer cells while not affecting normal cells [9-11].

References

1. Horton JK, Jagsi R, Woodward WA, Ho A. Breast cancer biology: clinical implications for breast radiation therapy. Int J Radiat Oncol Biol Phys. 2018;100(1):23-37.

2. Diaby V, Tawk R, Sanogo V, Xiao H, Montero AJ. A review of systematic reviews of the cost-effectiveness of hormone therapy, chemotherapy, and targeted therapy for breast cancer. Breast Cancer Res Treat. 2015;151(1):27-40.

3. Hongsheng G, Fenping W, Wang Y, Yan, C, Su W. Overexpressed ubiquitin ligase Cullin7 in breast cancer promotes cell proliferation and invasion via down-regulating p53. Biochem and Biophys Res Commun. 2014;450(4):1370-6.

4. Ahn HJ, Kim KS, Shin KW, Lim KH, Kim JO, Lee JY, et al. Ell3 stabilizes p53 following CDDP treatment via its effects on ubiquitin-dependent and independent proteasomal degradation pathways in breast cancer cells. Oncotarget. 2015;6(42):44523-37.

5. Guan YS, He Q, Zou Q. Status quo of p53 in the treatment of tumors. Anticancer Drugs. 2016;27(9):811-8.

6. Shepard B, Badley A. The biology of TRAIL and the role of TRAIL-based therapeutics in infectious diseases. Antiinfect Agents Med Chem. 2009;8(2):87-101.

7. James BR, Griffith TS. Tumor necrosis factor-related apoptosis-inducing ligand-induced apoptotic pathways in cancer immunosurveillance; molecular mechanisms and prospects for therapy. Research and Reports in Biochem. 2015;5:1-10.

8. Rahman M, Pumphrey JG, Lipkowitz S. The TRAIL to targeted therapy of breast cancer. Adv Cancer Res. 2009;103:43-73.

9. Ling J, Herbst RS, Mendelson DS, Eckhardt SG, Dwyer P, Ebbinghaus, et al. Apo2L/TRAIL pharmacokinetics in a phase 1a trial in advanced cancer and lymphoma. J Clin Oncol. 2006;24:3047.

10. Herbst R, Eckhardt G, Kurzrock R, Ebbinghaus S, O'Dwyer P, Gordon M, et al. Phase I dose-escalation study of recombinant human Apo2L/TRAIL, a dual proapoptotic receptor agonist, in patients with advanced cancer. J Clin Oncol. 2010;28(17):2839-46.

11. Yee L, Fanale M, Dimick K, Calvert S, Robins C, Ing J, et al. A phase IB safety and pharmacokinetic (PK) study of recombinant human Apo2L/TRAIL in combination with rituximab in patients with low-grade non-hodgkin lymphoma. J Clin Oncol. 2007;25:8078.

12. Manouchehri JM, Kalafatis M. Sensitization of rhTRAIL-resistant triple-negative breast carcinoma through silibinin co-treatment. Anticancer Res. 2017;37(12):6593-9.

13. Manouchehri JM, Turner KA, Kalafatis M. TRAIL-induced apoptosis in TRAIL-resistant breast carcinoma through quercetin co-treatment. Breast Cancer: Basic and Clinical Research Accepted Nov. 27, 2017, Pending publication:1–12.

14. Ashkenazi A, Pai RC, Fong S, Leung S, Lawrence DA, Marsters SA, et al. Safety and antitumor activity of recombinant soluble Apo2 ligand. J Clin Invest. 1999;104(2):155-62.

15. Lawrence D, Shahrokh Z, Marsters S, Achilles K, Shih D, Mounho B, et al. Differential hepatocyte toxicity of recombinant Apo2L/TRAIL versions. Nat Med. 2001;7(4):383-5.