Lei L Chen, J Cancer Sci Ther 2012, 4:10
http://dx.doi.org/10.4172/1948-5956.S1.022

OMICS Group Conferences
Accelerating Scientific Discovery

2nd World Congress on
Cancer Science & Therapy

September 10-12, 2012 Hilton San Antonio Airport, USA

Exploiting anti-tumor immunity to overcome relapse and improve remission duration

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Cancer survivors often relapse due to evolving drug-resistant clones and repopulating resilient tumor stem cells. Our preclinical study demonstrated that terminal cancer patient's lymphocytes can be converted from tolerant bystanders in vivo into effective cytotoxic T-lymphocytes in vitro killing patient's own tumor cells containing drug-resistant clones and tumor stem cells. We investigated a new strategy of combining targeted therapy (imatinib [IM, Gleevec®, Glivec®]) with immunotherapy (peginterferon α-2b [PegIntron®]) for treatment of stage III/IV gastrointestinal stromal tumor (GIST) with the rational that peginterferon α-2b serves as danger signals while IM's effective killing supplies GIST-specific-antigens in vivo without leucopenia, thus allowing for proper dendritic cell and cytotoxic T-lymphocyte differentiation toward Th1 adaptive cell-mediated immunity (Th1 response). Analysis of eight patients showed that this combination treatment is well tolerated, safe, and induced significant IFN-γ–producing–$CD8^+$, –$CD4^+$, –NK cells, and robust IFN-γ–producing-tumor-infiltrating-lymphocytes, signifying induction of innate and Th1 response. Complete remission (CR) + partial response (PR)=100%; overall survival=100%; one patient died of unrelated illness while in radiographic near-CR; after a median follow-up of 4 years (3.6 to 4.7 years), Six of 7 evaluable patients are either in continuing remission or showed progression-free-survival (PFS) more than doubling the median-genotype-specific PFS of the phase III IM-monotherapy trial (CALGB150105/SWOGS0033). We conclude that combination of non-marrow-suppressive-targeted therapy with immunotherapy is safe, induced significant innate and Th1 response, and demonstrated highly promising clinical efficacy in GIST model, thus warranting development in other tumor types including melanoma, prostate, breast, colon, pancreatic, and subsets of adenocarcinoma harboring EGFR mutations.

Biography

Lei L Chen received medical education at Albert Einstein Medical College, completed medical oncology fellowship at Memorial Sloan-Kettering Cancer Center. Prior to medical education, she worked as a post-doctoral fellow with Ralph Steinman at the Rockefeller University. Her most recent affiliations include MD Anderson Cancer Center (2000-2006) where she focused in sarcoma, gastrointestinal stromal tumor, completed pre-clinical studies, and designed the combination targeted therapy with immunotherapy; and Huntsman Cancer Institute, University of Utah (2006-2011) where she conducted the GIST study (DOI:10.1007/s00262-011-1185-1). She just retired—relinquishing clinical duties concentrating in research and planning of some of the clinical trials mentioned above.

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