Expanding the anticancer toolkit with evidence-based molecular-network-targeting: integrating natural products and off-label pharmaceutical agents in personalized anticancer therapy concurrent with, and independent of, radiation and chemotherapy protocols

J. William LaValley MD1,2,3

1Chairperson - Section of Integrative and Complementary Medicine, Doctors Nova Scotia, Canadian Medical Association, Chester, Nova Scotia, Canada; 2Travis County Medical Society, Texas Medical Association, Austin, Texas; 3Integrative MD Media, LLC, Austin, Texas, USA

BACKGROUND:
The purpose of the study is to describe the clinical integration of anticancer treatment options via administration of chemotherapy and/or radiation therapy with multiple molecularly-targeted natural products (NPs) and off-label pharmaceutical agents (OLPAs) for personalized anticancer treatment. Recently, increasing clinical interest in molecular network targeting provides promising clinical options for additional evidence-based anticancer treatments.

METHODS:
Using an advanced proprietary cancer molecular biology database developed by the author, linked to the PubMed literature evidence-base, molecular targets for various cancers are identified for molecular anticancer intervention. Natural products (NPs) and off-label pharmaceutical agents (OLPAs) with molecular target anticancer activity are identified for relevance to patients’ pathological cancer diagnosis. Emphasis is on molecular network targeting, in which single therapeutic NPs and OLPAs exert anticancer activity on multiple different molecular targets, and in which specific molecular targets respond to activity of multiple different NPs and OLPAs. NP and OLPA recommendations are implemented through efficient flexible patient-centric administration schedules. The NPs and OLPAs are offered in addition to - not instead of - conventional chemotherapy and/or radiation therapy. Treatment with NPs and OLPAs can occur in conjunction with, or away from, chemotherapy and/or radiation therapy. Treatment goals for clinical administration of NPs and OLPAs in conjunction with conventional chemotherapy and/or radiation therapy are to provide increased, or synergistic, anticancer effect of chemotherapy and/or radiation therapy, without interferring with the molecular mechanisms of anticancer action of the chemotherapy and/or radiation therapy. Molecular target mechanisms increase chemosensitivity (decrease chemoresistance) and increase radiosensitivity (decrease radioresistance) in cancer cells while concurrently decreasing adverse clinical effects experienced by the patients. Multi-agent, multi-target anticancer treatment recommendations are developed using the database with emphasis on targets identified via patient-specific pathologic markers, genomic and/or proteomic test results or, in cases without genomic/proteomic testing results, on likely molecular targets in the cancer cell genome.

RESULTS:
Three human patient case study examples include pancreatic adenocarcinoma stage IIb, glioblastoma stage IV, and melanoma stage IV. Selected treatment recommendations demonstrate effective usage of the database to integrate numerous concurrent treatment options including multiple NPs and OLPAs in a safe, practical and beneficial manner. Anticancer molecular target indications for several NPs and OLPAs are identified. Specific examples of dosage ranges and administration schedules of these evidence-based, multi-agent, molecular-network-targeted protocols are shown. Protocols shown include multiple NPs and OLPAs administered concurrent with, and independent of, chemotherapy and/or radiation therapy.

CONCLUSIONS:
The currently available evidence-base is utilized to develop and integrate multi-agent, multi-target clinical anticancer treatment protocols including natural products and off-label pharmaceutical agents for administration concurrent with, and independent of, conventional anticancer chemotherapy and/or radiation therapy. These molecular-network-targeted protocols provide increased personalized anticancer therapeutic activity for patients diagnosed with cancer.

CLINICAL GOAL:
To provide additional evidence-based, molecularly-targeted, well-tolerated anti-cancer clinical benefit using multi-targeted multi-agent protocols in addition to - not instead of - conventional chemotherapy, radiation therapy and surgery.

DATABASE IDENTIFIES MOLECULAR RELATIONSHIPS AND POTENTIAL SYNERGIES

Cancer Types

Interactions

Organ &/or cell types

Anti-Cancer Molecular Targets

Chemotherapy & Biologics

Anti-Cancer Natural Products

Anti-cancer Off-label Pharmaceuticals Agents

CLINICAL EXAMPLES OF THREE PATIENTS

Example of Molecular-Networks: Selected Target Anti-Cancer Activity of Several Common Natural Products

Evidence supports clinical consideration of

- administration of various specific natural products for anti-cancer effect against many cancer cell types and many cancer molecular targets
- administration of multiple concurrent natural products for extended durations in metronomic-like daily dosage schedules
- administration of multi-agent multi-target anti-cancer natural product protocols before and after completion of chemotherapy and radiation therapy providing extended, sustained molecularly-targeted anti-cancer treatment
- administration of appropriately selected natural products are well-tolerated for extended durations

EX: Curcumin, Resveratrol, EGGc, Silimarin, Gemcitabine [Refs: many contact author]

Evidence supports clinical consideration of

- administration of various specific molecularly-targeted re-purposed off-label pharmaceutical agents (OLPAs) for anti-cancer effect against many cancer cell types and multiple cancer molecular targets
- administration of multiple concurrent OLPAs for extended durations of metronomic-like daily dosage schedules
- administration of multi-agent multi-target anti-cancer OLPAs before and after completion of chemotherapy and radiation therapy providing extended, sustained molecularly-targeted anti-cancer treatment
- administration of appropriately selected OLPAs are well-tolerated for extended durations

EX: Rx-Metformin and multiple anti-cancer molecular targets; PMID: 2533103; PMID: 24204085; PMID: 2383693; others
EX: Rx-Celecoxib and multiple anti-cancer molecular targets; PMID: 2239342; PMID: 2083693; others

Evidence supports clinical consideration of

- administration of various specific natural products concurrent with various specific chemotherapy agents to enhance cancer cell chemosensitivity to those chemotherapy agents; numerous in-vivo and in-vitro data [PMID: 20924967; PMID: 21261654; others]

EX: Curcumin chemosensitizes pancreatic adenocarcinoma cells to gemcitabine chemotherapy [PMID: 1782652]

Evidence supports clinical consideration of

- administration of various specific off-label pharmaceutical agents concurrent with radiation therapy to enhance cancer cell radiosensitivity; various in-vitro and in-vivo data [PMID: 17293239]
EX: Rx-Celecoxib enhances radiosensitivity of glioblastoma cells in vitro and in vivo [PMID: 18572701]
EX: Rx-Celecoxib enhances radiosensitivity in glioblastoma w/or w/o Temozolomide [PMID: 21362131]; improves overall survival [PMID: 23523186]

For further detailed references, discussion, comment, collaboration:
Contact: J. William LaValley MD
Medical Wellness Plan®: 6301 Pathfinder Dr., Austin, TX 78759
Ph: 512-794-8907 MedicalWellnessEastlink.ca
Fax: 512-717-9075 © J. William LaValley MD 2014

Society for Integrative Oncology Conference
Houston, TX 26-28 October 2014

CLINICAL EXAMPLES OF THREE PATIENTS

- Therapy
- 1: Rx-Metformin and multiple anti-cancer molecular targets; PMID: 2533103; PMID: 24204085; PMID: 2383693; others
- 2: Rx-Celecoxib and multiple anti-cancer molecular targets; PMID: 2239342; PMID: 2083693; others
- 3: Rx-NSAIDs and multiple anti-cancer molecular targets; PMID: 24204085; PMID: 2383693; others

- Rx Metformin 500 mg day
- Rx Celecoxib 200 mg day
- Rx Naproxen 220 mg day

- Duration
- 1: 4 weeks
- 2: 4 weeks
- 3: 4 weeks

- Change
- 1: 500 mg day
- 2: 200 mg day
- 3: 220 mg day

- Days
- 1: 28 days
- 2: 28 days
- 3: 28 days

Evidence supports clinical consideration of

- administration of various specific natural products concurrent with various specific chemotherapy agents to enhance cancer cell chemosensitivity to those chemotherapy agents; numerous in-vivo and in-vitro data [PMID: 20924967; PMID: 21261654; others]