

Chapter 8

Combinational Therapy Using Chemotherapeutic Agents and Dietary Bioactive Compounds: A Pragmatic Approach to Cancer Treatment

Madhumitha Kedhari Sundaram

Manipal Academy of Higher Education, UAE

Shefina Silas

Manipal Academy of Higher Education, UAE

Arif Hussain

Manipal Academy of Higher Education, UAE

ABSTRACT

Diet-derived phytochemicals find prominent use in traditional medicine and have been credited with lowering cancer risk significantly. Dietary agents demonstrate anticancer activity by modulating various molecular targets and cell signaling pathways. Several studies have focused on combinations of dietary bioactive compounds and conventional chemotherapeutic agents to augment their therapeutic response and mitigate the side effects of conventional chemotherapy. The observed synergistic response heralds promise for successful future chemopreventive and chemotherapeutic strategies in cancer management. Animal models and pre-clinical trials of the effective combinations must be undertaken to clearly understand the mechanism of action. This chapter catalogues recent studies that have used dietary bioactive compounds (sulforaphane, EGCG, curcumin, genistein, resveratrol, eugenol) in combination with conventional chemopreventive agents and with other phytochemicals.

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INTRODUCTION

Cancer is a multi-step, multi-factorial disorder that continues to claim numerous lives across the world each year. A cancer cell is characterized by its ability to achieve replicative immortality, unrestricted proliferation, capacity to invade, migrate, form new blood vessels, alter their energetics and promote inflammation (Hanahan & Weinberg, 2000, 2011). Inflammation and genomic instability are pertinent enablers of carcinogenesis, while altered energetics and immune response are being considered as emerging hallmarks of cancer. These capabilities are dependent on their ability to alter several growth-signaling pathways, death inducing pathways and cell regulatory pathways. The molecular biology that underlies these competencies are represented by two main classes of genes; the oncogenes and the tumour suppressor genes (TSGs) including those involved in DNA repair (Burstein & Schwartz, 2008; Herceg et al., 2018). While epigenetic mechanisms are at the centrestage of normal development, any abnormality alters cellular function by disturbing the balance between various proteins and regulators in the cells. Changes in the key regulators, leads to modifications in the epigenetic patterns impacting gene expression and results in development of malignancies (Soto, Song, & McLaughlin-Drubin, 2017). Alteration in epigenetic mechanisms including DNA methylation and histone modifications fuel widespread changes in expression of TSGs and oncogenes (Sharma S, Kelly TK, 2010). An ideal therapeutic strategy would be to target one or more of these cancer hallmarks and induce cell death.

Significant understanding of the biology of cancer has been achieved and several treatment avenues have been developed. Despite the huge advancements in diagnosis and treatment, cancer is responsible for a significant number of human mortality with more than 9.6 million people succumbing to it in 2018 alone (Bray et al., 2018). The number of new cancer incidences is set to increase to 22 million and a major proportion of them are expected in the developing countries of Africa, Asia, and Central and South America (Jacques Ferlay et al., 2015). In India, it is expected that more females (712,758) than males (679,421) will be affected in 2020, with 98.7 per 100,000 population affected (Mathur et al., 2020). It is estimated that if the risk factors such as tobacco, infection are modified then nearly 70% of cancers incidence across India can be prevented (Gandhi, Kumar, Bhandari, Devnani, & Rath, 2017). This highlights the need for comprehensive health care guidelines and the importance of healthy diet and lifestyle practices. In terms of both cancer incidence and mortality, cancers of the breast, lung and cervix are the top three respectively, amongst women across the globe (J. Ferlay et al., 2019). While for men, cancers of the lung, prostate and stomach have the highest incidence and cancers of the lung, liver and stomach have the highest mortality (J. Ferlay et al., 2019). Therefore, considerable attention needs to be given to the development of effective cancer treatments.

Chemotherapeutics And Its Limitations

For almost 60 years now, chemotherapeutic drugs have endured as the keystone of cancer treatment (DeVita & Chu, 2008). Despite, being the gold standard of treatment, high level of success has been elusive. Chemotherapeutic agents are capable of disrupting the cell cycle and reduce cell proliferation (Tao, Visvanathan, & Wolff, 2016). Further, they promote the onset of apoptosis, leading to cancer cell death. A similar mechanism of action is displayed by the majority of chemotherapeutic agents. Unfortunately, conventional cancer therapies and existing epigenetic modifiers are characterized by low specificity with non-specific action towards all rapidly dividing cells, resulting in substantial cellular and clinical toxicity and/or poor quality of life for the patient (Aslam et al., 2014; Beaver & Magnan, 2016; Chan &

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