Journal of Clinical Toxicology
ISSN: 2161-0495

Kumar et al., J Clin Toxicol 2019, 9:3

Editorial Open Access

Chemotherapy-Associated Genomic Toxicity and Future of Cancer Treatment

Subodh Kumar[1], **Nikhil C Munshi**[1,2] **and Masood A Shammas**[1*]

[1]*Harvard (Dana Farber) Cancer Institute and VA Healthcare System, West Roxbury, USA*

[2]*Harvard Medical School, Boston, USA*

[*]***Corresponding author:*** *Masood A Shammas, Harvard (Dana Farber) Cancer Institute & VA Boston Healthcare System, West Roxbury, MA 02132, USA, E-mail: masood_shammas@dfci.harvard.edu*

Received date: May 20, 2019; **Accepted date:** June 11, 2019; **Published date:** June 18, 2019

Citation: Kumar S, Munshi NC, Shammas MA (2019) Chemotherapy-Associated Genomic Toxicity and Future of Cancer Treatmen. J Clin Toxicol 9: e126.

Editorial

Cancer genome is usually unstable and, therefore, constantly acquires changes at both the nucleotide sequence as well as chromosomal levels [1-3]. Ongoing genomic changes, which confer new characteristics to the recipient cells, underlie their progression to advanced disease states including acquisition of drug resistance and treatment failure. Data from our laboratory have shown that increased number of mutations correlates with poor survival of myeloma patients [2]. One of the consequences of genomic instability and increased mutational burden can also be the formation of more neo-antigens which help recognition of cancer cells as non-self by immune system. However, continued acquisition of genomic changes can also give new characteristics to cancer cells which may help them escape immune surveillance [4]. Consistent with unstable genome, cancer cells display a number of genomic aberrations including increased levels of spontaneous DNA breaks. Using esophageal adenocarcinoma and multiple myeloma as model systems, we have shown that homologous recombination, the most precise DNA repair mechanism, is dysregulated (or spontaneously elevated) in cancer cells and contributes to ongoing genomic evolution [3,5], drug resistance [3] and growth of cancer cells in subcutaneous tumor model [6]. We have recently also shown that apurinic/apyrimidinic nucleases (APEX1 and APEX2) contribute to increased DNA breaks and homologous recombination activity in myeloma cells [7]. Cancer drugs which are genotoxic or induce DNA damage or breaks, either directly or indirectly, kill cancer cells by increasing the damage to their DNA. However, following such treatments the subsets of cancer cells which survive (and not killed by) as well as normal cells of the patient now have increased levels of DNA damage and breaks. This aspect of chemotherapy poses a risk of development of resistance to treatment in cancer cells and transformation of normal cells. Consistent with this view, we have shown that melphalan, a chemotherapeutic agent, induces homologous recombination activity and genomic instability in myeloma cells in vitro [7]. Similarly, certain chemotherapeutic agents have been linked to development of secondary cancers [8,9]. There are also reports which suggest that chemotherapy has higher likelihood of contributing to development of leukemia as compared to radiation. It is, therefore, necessary to develop drugs which target mechanisms underlying increased genomic damage and instability in cancer cells. Such drugs have potential to inhibit/delay progression by reducing genomic instability and evolution. There is also evidence that such drugs may have ability to increase cytotoxicity while minimizing/reducing genomic toxicity caused by chemotherapeutic agents [7].

Acknowledgement

Research work in our laboratory is supported by Department of Veterans Affairs Merit Review Award I01BX001584-01 (NCM), NIH grants P01-155258 and 5P50 CA100707 (MAS, NCM) and Leukemia and Lymphoma Society translational research grant (NCM).

References

1. Lee JK, Choi YL, Kwon M, Park PJ (2016) Mechanisms and consequences of cancer genome instability: lessons from genome sequencing studies. Annu Rev Pathol 11: 283-312.
2. Bolli N, Avet-Loiseau H, Wedge DC, Van Loo P, Alexandrov LB, et al. (2014) Heterogeneity of genomic evolution and mutational profiles in multiple myeloma. Nat Commun 5: 2997.
3. Shammas MA, Shmookler Reis RJ, Koley H, Batchu RB, Li C (2008) Dysfunctional homologous recombination mediates genomic instability and progression in myeloma. Blood 113: 2290-2297.
4. Nandi B, Talluri S, Kumar S, Yenumula C, Gold JS, et al. (2019) The roles of homologous recombination and the immune system in the genomic evolution of cancer. J Transl Sci 5: 1-7.
5. Pal J, Bertheau R, Buon L, Qazi A, Batchu RB, et al. (2011) Genomic evolution in Barrett's adenocarcinoma cells: Critical roles of elevated hsRAD51, homologous recombination, and Alu sequences in the genome. Oncogene 30: 3585-3598.
6. Lu R, Pal J, Buon L, Nanjappa P, Shi J, et al. (2014) Targeting homologous recombination and telomerase in Barrett's adenocarcinoma: Impact on telomere maintenance, genomic instability, and tumor growth. Oncogene 33: 1495-1505.
7. Kumar S, Talluri S, Pal J, Yuan X, Lu R, et al. (2018) Role of apurinic/apyrimidinic nucleases in the regulation of homologous recombination in myeloma: mechanisms and translational significance. Blood Cancer J 8: 1-10.
8. Nutalapati S, Jain SR (2018) Risk of second malignancies in breast cancer patients who received chemotherapy: A SEER analysis. J Clin Oncol 36: 1565.
9. Brower V (2013) Tracking chemotherapy's effects on secondary cancers. J Natl Cancer Inst 105: 1421-1422.