Computer Simulation of Effective Intermittent Chemotherapy for Colon Cancer

David E. Axelrod[1], Sudeepti Vedula[2], and James Obaniyi[3]

Short Abstract – Chemotherapy against early colon cancer was simulated with an agent-based computer model. Normal cells in colon crypts could tolerate higher intermittent dose schedules than constant schedules. Intermittent high doses could eliminate drug-resistant mutant cells while retaining normal cell dynamics in a functional crypt.

Key words - Drug resistance, Heterogeneity, Dose schedules, Intermittent, Colon cancer, Adenoma, Crypt

I. Purpose

The effectiveness of cancer chemotherapy is limited by intra-tumor heterogeneity, the emergence of spontaneous and induced drug-resistant mutant cells, and the maximum dose to which normal tissues can be exposed without adverse side effects. The goal of this project was to determine if these limitations could be overcome by intermittent schedules of the maximum dose that allows colon crypt maintenance; specifically by eliminating mixtures of drug-resistant mutant cells from heterogeneous early colon adenomas while maintaining colon crypt function.

II. Methods

An agent-based computer model of cell dynamics in human colon crypts was developed. The model was calibrated with the number of quiescent stem cells, proliferating cells, and non-proliferating differentiated cells measured in human biopsy specimens. Details of image acquisition, measurements by image analysis, and determination of reliability of measurements were previously described in detail [1]. The model allowed simulation of continuous and intermittent dose schedules of a cytotoxic chemotherapeutic drug, as well as determining the effectiveness of a drug on the elimination of mutant cells and the maintenance of crypt function. The open-source model **Colon Crypt Model 110514 G. nlogo** is available to download at http://dx.doi.org/doi:10.7282/T3KH0QKV. The model was produced with the open-source multi-agent modeling environment NetLogo application available at http://ccl.northwestern.edu/netlogo.

III. Results

Colon crypts can tolerate a tenfold greater intermittent dose than constant dose of a cytotoxic chemotherapeutic drug. Intermittent dose schedules can eliminate both fast growing drug-sensitive and slow growing drug-resistant cells in a heterogeneous crypt with a mixture of mutant cells. Intermittent doses schedules can eliminate spontaneously evolving mutants in a heterogeneous crypt. Intermittent dose schedules can also eliminate drug-induced mutants in a heterogeneous crypt [2].

IV. Conclusions

An intermittent dose of a cytotoxic drug, at the maximum that allows colon crypt maintenance, can be effective in eliminating a heterogeneous mixture of mutant cells before they fill the crypt and form an adenoma. Mutants can be eliminated whether they arise spontaneously or are induced by a cytotoxic drug

References

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Acknowledgments: Funded by the Human Genetics Institute of New Jersey, the BCR Fund at Rutgers University, and the Rutgers Cancer Institute of New Jersey (PA30iCA072720).

[1]Department of Genetics and Cancer Institute of New Jersey, Rutgers University, 604 Allison Road, Piscataway, NJ 08854-8082, USA. Email: axelrod@biology.rutgers.edu

[2]Department of Molecular Biology and Biochemistry, and Department of Biomedical Engineering, Rutgers University, 599 Taylor Road, Piscataway, NJ 08854, USA. Email: sudeepti.vedula@rutgers.edu

[3]Department of Biomedical Engineering, Rutgers University, 599 Taylor Road, Piscataway, NJ 08854, USA. Email: jobaniyi65@gmail.com