Computer Simulation of Colon Cancer Chemoprevention

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***Short Abstract* — A calibrated computer model was developed for cell kinetics in human colon crypts. Simulations indicated that colon cancer may be prevented by intermittent doses of a drug that induces cell death at the top of the crypt.**

***Keywords* — colon cancer, chemoprevention, intermittent treatment, adenoma, computer simulation**

I. Purpose

Effective chemoprevention of cancer requires choices of (*i*) an agent(s) that is effective with little or no undesirable effects, (*ii*) patients who would benefit from the exposure to the agent, and (*iii*) dose intensity and dose schedules that maximize the prevention effect and minimize negative side effects. The purpose of this project was use a computer model of cell kinetics in human colon crypts to determine the maximum dose intensity and intermittent pulse dose schedules of a chemoprevention drug that would be effective in preventing colon cancer.

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, reliability of measurements, and confirmed behavior of the model were previously described [1]. The "Colon Crypt Model 031215.nlogo" is available to download at http://dx.doi.org/doi:107282/T3TQ638W. The model program runs on the open-source multi-platform NetLogo application version 4.1.3, or 5.3.1 available to download at http:ccl.northwestern.edu/netlogo/. The model allowed simulation of continuous and intermittent dose schedules of a chemoprevention drug, such as sulindac that induces apoptosis at the lumen surface of the crypt. Parameter sweeping indicated the effect of various dose durations, intervals, and intensities on the effectiveness of drug treatment in removing mutant cells before they can form an adenoma, while retaining crypt function.

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III. Results

In normal colon crypts, quiescent stem cells at the bottom of the crypt may become active stem cells and divide. The progeny cells move up the crypt, continue to divide, differentiate, and are removed at the top of the crypt. Mutant cells, if they have a higher probability of dividing than normal cells, may proliferate and fill the crypt before they can be removed at the top, forming an adenoma that is an early stage of colon cancer. Sulindac is a drug that alters crypts by increasing the probability that both normal cells and mutant cells at the top of the crypt will die by apoptosis and be removed. Sulindac can be applied to crypts as a chemopreventive drug before the appearance of mutants. It makes crypts inhospitable to mutant cells rather than killing mutant cells. Simulation results indicated that treatment of a crypt before a mutant cell arises can decrease the probability that a mutant cell will proliferate, fill the crypt and form an adenoma. Crypts treated with intermittent pulse schedules have three times the maximum tolerated dose than crypts treated with constant dose schedules, and have a 10-year delay in the appearance of adenomas. This results in chemoprevention by delay.

IV. Conclusions

Intermittent pulses of a drug that induces apoptosis at the top of a colon crypt could allow an increased maximum tolerated dose compared to a constant dose, and could result in chemoprevention of colon cancer.

References

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