S27. Prevention of colorectal polyps by DMFO and Sulindac

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Polyamines are actively involved in proliferation and differentiation of many tissues. Lowering of intracellular levels via inhibition of the initial step (ornithine decarboxylase) in the polyamine synthesis pathway by the specific enzyme-activated inhibitor difluoromethyl-ornithine (DFMO) results in a decrease of adenomas and cancers in many preclinical organ-site models, most notable in the colon. From 1989–1997 we conducted a series of pilot, Phase IIa and Phase IIb trials. We determined the lowest dose at which polyamine content of the colonic flat mucosa would be significantly lowered. In 1997 we considered whether to do a definitive trial with DFMO alone or to combine it with another chemopreventive compound. We decided to combine DFMO with the NSAID Sulindac at a low dose for a variety of mechanistic, experimental, and clinical reasons. We began a Phase IIb trial in which the recurrence of adenomas would be correlated with polyamine changes in flat mucosa. Several years later it was expanded to a Phase III trial in which recurrence of adenomas became the primary endpoint. The Data and Safety Monitoring Board recommended a second interim analysis after 70% of subjects had completed their 3-year or off-study colonoscopy. They determined that the study could be stopped as the efficacy goals had been met. Overall, a highly significant reduction of 67% of all adenomas ($p < 0.0001$) and 92% of all advanced adenomas ($p < 0.0005$) was seen. Levels of both putrescine and spermidine in rectal mucosal biopsies were also markedly reduced in the active intervention arm, after both 12 and 36 months. Prostaglandin E2 (PGE2) levels were unaffected. Toxicities were carefully monitored for all adverse events. Hematologic, gastrointestinal and cardiovascular toxicities were analyzed individually and in a number of ways; clinical toxicities were low and comparable in the two arms. Careful serial audiograms showed subclinical changes that were more frequent in the active intervention arm, with some reversals after six months off drugs. An updated final report will be presented and will include off study colonoscopies and adverse events in subjects who were still on study at the time of the second interim analysis. Larger trials will be needed to determine the absolute risk of cardiovascular events and audiologic changes with this regimen. Longer term studies will also be needed to determine whether the absolute endpoint of colorectal cancer incidence can be reduced.