More Letters

Cardiac Glycosides vs Alkylating Agents in Medical Oncology

Editor:

The title may seem strange as alkylating agents were introduced already in the 1940s to treat lymphomas, whereas cardiac glycosides still are not used in cancer therapy, or perhaps they are, but not in pure form but as constituents of herbal extracts and other natural products. I see a great potential to find more effective and less toxic therapies for cancer by thinking in these terms.

My interest in the Coley toxins propelled me into oncology; 10 years ago I got to know Helen Coley Nauts, DSc, founder of Cancer Research Institute, NYC.[1] Through her I have learned about Wayne Martin. He needs no introduction to the readers of *TLfDP* as his frequent reports are always intriguing reading. In fact, without information from Wayne I would not have started experiments with digitalis on cancer cell lines and the movement in this area seen recently would probably not had started, at least not now.

Wayne told me about anticancer effects of Foxglove extracts, i.e. digitalis. That was information he got during his studies at Purdue University in the 1930s. As I am studying apoptosis it seemed worthwhile to explore this statement experimentally, as the major known effect of the cardiac glycosides is Na+/K+ATPase inhibition which leads to increased intracellular Ca2+ concentration, and that is a crucial step in apoptosis induction.

When I applied the common clinically used cardiac glycosides digitoxin and digoxin to leukemic cell lines, the effects were striking; potent apoptosis induction. This occurred in therapeutic plasma concentrations for treating cardiac disease. Even more intriguing was that highly proliferating normal cells were not affected at all. Digitoxin was much more potent than digoxin in these in vitro experiments.[2] I contacted Björn Stenkvist, MD, PhD, who had reported anticancer effects of digitalis in women operated for breast cancer when taking the drug (almost all on digoxin) due to cardiac disease.[3] He told me that as he had done this very encouraging observation he tried to initiate studies on anticancer effects of digitalis, but there was no interest. However, when seeing the apoptosis induction in our studies, he was encouraged and made a re-analysis of the women in his study and still detected an anticancer effect.[4]

Now we have examined several cancer cell lines and digitoxin is a potent inhibitor of proliferation and inducer of apoptosis.[5] Recently, a group in M.D. Anderson Cancer Center confirmed our results concerning apoptosis induction in cancer prostate cells, by digitalis, published earlier this year.[6] This group has focused on a patented extract of Oleander (Anvirzel).[7] Ralph Moss gives some of the background to Anvirzel in the excellent book *Herbs Against Cancer*. Oleander contains the cardiac glycoside oleandrin that is very similar in chemical structure to digitoxin. Instead of explaining the anticancer effects of Anvirzel with "immune-stimulating properties," an anticancer effect of oleandrin in Anvirzel is now proposed.[7]

We have found that the fraction of cancer cells surviving digitalis treatment accumulate in the G2M phase of the cell cycle. Cells are more susceptible for irradiation in this phase. We also found an increased radiosensitivity in breast cancer cell lines treated with digitoxin.[8]

Apoptosis is a very hot topic in cancer research. It is now evident that high proliferation rate is not the main problem in cancer, but impaired apoptosis. High proliferation rate of cells is normal in certain circumstances. An example is infection when immune competent cells may increase enormously and downregulate when the infectious agent is cleared away. If the apoptosis mechanisms work properly, high proliferation rate is never a problem.

Cardiac glycosides induce apoptosis in several cancer cell lines, sparing even normal cells with high proliferation rate, i.e. showing a specificity for cancer cells. They seem to work in all phases of the cell cycle. This is interesting to contrast with the observation that led to the introduction of alkylating agents in oncology in the 1940s; bone marrow and lymphoid hypoplasia in healthy people exposed to mustard gas.[9] Since then numerous derivates of alkylating agents have been introduced. Still, the newer derivates are not specific for cancer cells but hit highly proliferating cells indiscriminately. Unfortunately, cancer cells often have a lower proliferation rate compared to the normal tissue, thus side effects are dose-limiting. It seems difficult to develop cancer specific derivates of a drug originally observed for inducing cell death in normal cells.

The in vitro data accumulated up to now show properties of the cardiac glycosides more or less perfect to treat some types of cancer. Clinical studies will reveal if this turns out to be reality.

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