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Mini Review

Digitoxin has Specific Properties for Potential use to Treat Cancer and Inflammatory Diseases

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Abstract

New knowledge about diseases on the molecular level demonstrates that inflammation is a common determinant for seemingly very different disorders. Long standing high levels of pro-inflammatory cytokines is an important factor also for cancer. In fact, the pro-inflammatory cytokines may stimulate normal cells, such as immune cells and fibroblasts, to produce more growth factors and cytokines that the cancer cells take advantage of and a vicious circle occurs. More focus is now on this interaction in cancer research and how to break it. Pancreas cancer is a typical example with a lot of stroma in relation to the cancer cells. Cardiac glycosides, especially in the form of digitoxin, have very interesting properties when it comes to target these mechanisms on the molecular level.

Keywords: Cardiac Glycosides; Digitoxin, Apoptosis; Cancer, Pancreas; Glioblastoma; Cholangiocarcinoma

Abbreviations: NK: Natural Killer; PD-L1: Programmed Death-1-Ligand; CNS: Central Nervous System; EGFR: Epidermal Growth Factor Receptor; NF-κB: Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B Cells; CAFs: Cancer-Associated Fibroblasts; TGF-β: Transforming Growth Factor Beta; IL-6: Interleukin-6; TNF-α: Tumor Necrosis Factor Alpha

Introduction

The innate immune system plays a pivotal role for eradicating cancer cells in humans. Apoptosis (programmed cell death) in cancer cells triggered by immune cells, such as human NK cells, is a mechanism for the human body to get rid of malignant cells [1]. During studies how to strengthen the innate immune system against cancer we found that cardiac glycosides, digoxin and digitoxin, are potent inducers of apoptosis in different types of cancer cells in doses that are not toxic for humans. Actually, we were the first to show apoptosis in cancer cells by digitalis [2,3]. The last years several new molecular modes of action of the cardiac glycosides of impact for cancer and inflammatory diseases have been shown. Clinical studies of digitalis for cancer are ongoing and in progress, however, almost all use digoxin [4]. Our data indicate that digitoxin has more potent anti-cancer effects, in concentrations that are non-toxic for humans, than digoxin [2-6]. Digitoxin is of interest to use as single agent and in combination with chemotherapy in clinical cancer trials and may also be valuable to suppress harmful inflammatory reactions. Digitoxin may also be combined with radiotherapy and/or new antibodies, such as PD-L1 antibodies, to enhance the anti-cancer effects. This mini-review summarizes some of the most interesting properties of the cardiac glycosides from a clinical point of view.

Background

William Withering made digitalis a common drug to treat cardiac congestion by his book. "An account of the Foxglove and some of its Medical uses with practical remarks on the dropsy, and other diseases", published in 1785. Digitalis extract had been used in folk medicine much earlier, but Withering's observations led to a more rational use. Plant extracts containing cardiac glycosides, for example from Nerium Oleander, have been documented in remedies against cancer as early as in the Middle Ages from different parts of the world [3]. Today digitalis, in the form of the cardiac glycosides digoxin and digitoxin, is used to treat cardiac congestion and some arrhythmias, however, the use is decreasing and digitoxin has been taken off the markets in many countries as it has been replaced

by other cardiac drugs. Generally, digoxin is regarded easier to dosage than digitoxin and digoxin has been more common to use than digitoxin. Digoxin has a shorter half-life than digitoxin. The chemical difference is that digoxin has an extra hydroxyl group (-OH) compared to digitoxin; i.e. digoxin is more hydrophilic and is excreted by the kidneys. Digitoxin is mainly metabolized in the liver and excreted by the faeces. Digitoxin is lipophilic and pass the blood-brain barrier and reach the CNS and higher than plasma concentrations in the liver, kidneys, brain and heart [3]. The renal function has a" normal decline" by increasing age, in contrast to liver function, and most patients with cardiac congestion are older, thus, digitoxin may be safer in this patient population [7]. Recently, a debate among cardiologists has started; maybe digitalis has been replaced too early by newer drugs. Studies comparing the newer cardiac drugs to digitalis are lacking [8]. Digitalis has the unique capability to increase the inotropic effect of the cardiac muscle without increasing the oxygen consumption. Interestingly, healthy volunteers taking digitoxin in therapeutic dose for treating cardiac congestion, had reduced diastolic blood pressure and heart rate during overnight sleep, probably because of increased parasympathetic activity or decreased sympathetic activity [9]. Time will show if digitoxin will have a renaissance in cardiology.

Properties of Cardiac Glycosides Pivotal for Cancer and Inflammation

Jens C. Skou made the first discovery of an ion-transporting enzyme, the ubiquitous plasma membrane Na+/K+ ATPase in 1957. The main pharmacological effect of clinical benefit of the cardiac glycosides seemed to be inhibition of the Na+/K+ ATPase on cardiac muscle cells and the subsequent ion changes with increased intracellular calcium ion concentration leading to a positive inotropic effect on the heart. Since we reported apoptosis in cancer cells by cardiac glycosides, it has become obvious that the Na+/K+ ATPase have two distinct roles; the well known as an ion pump and in addition as a protein-protein signal transducer. Increased intracellular calcium ion concentration is a part of the apoptotic cascade and in addition the Na+/ K+ ATPase signals through several other signaling pathways that regulate apoptosis and proliferation, such as through the pathways of EGFR and other tyrosine kinase receptors [10]. Notably, digitoxin is a strong inhibitor of the transcription factor NF-κB and can abolish the production of pro-inflammatory cytokines [11]. The tumor micro-environment and stroma directly influences the progression of solid tumors through secretion of growth factors and extracellular matrix depositions. CAFs support angiogenesis and cancer cell invasion and metastasis. TGF-β from cancer cells start differentiation of fibroblasts to CAFs. This mechanism seems to be present for different types of solid tumors, such as glioblastoma, pancreas cancer, prostate cancer and also for several hematological malignancies. Pro-inflammatory cytokines such as IL-6 and TNF-α are often involved in this interplay between the cancer cells and stroma cells as well [12-15]. Cardiac glycosides have the ability to inhibit this process [11,12,16]. The capability of digitoxin to inhibit NF-κB and by that abolish the pro-inflammatory cytokines, may be useful for an array of chronic inflammatory disorders such as ulcerative colitis, Crohn´s disease, systemic sclerosis among other diseases. However, real high levels of the pro-inflammatory cytokines may be acute life threatening. The bird flu virus, H5N1, killed many young healthy adults with intact immune systems. The main cause of death of these individuals were respiratory distress caused by a "cytokine storm", hyper-production of pro-inflammatory cytokines; the immune system overreacted towards the virus [17,18]. It was great concern during the H5N1 epidemic how to handle the situation as the accessible antiviral drugs were not very effective. It would be worthwhile to evaluate digitoxin in this context if such a situation occurs again and we do not have any other effective drugs.

Digitoxin makes the cancer cells immunogenic, especially in combination with some type of chemotherapy [19,20]. The immunogenic effect of digitoxin as well as the inhibition of IL-6 and similar pro-inflammatory factors may make digitoxin an effective combination with newly developed PD-L1 antibodies [21]. In addition, we and others have shown a radio-sensitizing effect of cardiac glycosides on cancer cells [3]. Naturally, one wonder if all these interesting molecular effects of the cardiac glycosides are clinically relevant. Epidemiological studies may give some indications. We examined a population of more than 9000 patients on digitoxin for cardiac disease and correlated to data in the Norwegian Cancer Registry. This population has serious cardiac disease and eventual anti-cancer effects may be masked behind the high morbidity and mortality due to the cardiac conditions. Still, significant anti-cancer effects were detected for leukemia/lymphoma and urothelial and kidney cancer [22]. Several epidemiological studies on digitalis and cancer have been done, most concerning digoxin, and the results differ considerably. Some studies find anti-cancer effects, others not, some studies indicate an increased risk for cancer in a population on digitalis [23-25].

It has been hypothesized that the anti-cancer effect of digitalis is due to an estrogen effect and that this estrogen effect also could increase the risk for some cancers [26]. However, in our experiments we found estrogen expressing breast cancer cells to be less sensitive for digitoxin compared to receptor negative breast cancer cells [3]. Recent data confirm that mechanisms other than interaction with hormone receptors are the main effect of digitalis on breast cancer cells [27].

Digitoxin has complex dose dependent mechanisms of action; lower concentrations may induce transcription of survival genes whereas higher concentrations can induce cell death by caspase activation and apoptosis and even higher concentrations induce cell death through necrosis due to heavily disrupted ion homeostasis. Digitoxin seems to target several signaling mechanisms of crucial roles for cancer cells simultaneously and that might make it more difficult for the cancer cells to develop resistance [3,10].

Conclusion

Despite the vast number of in vitro studies, epidemiological studies and clinical cancer studies done the last 10+ years, still we do not know if any cardiac glycoside will have a role in oncology. Most of the clinical studies so far are on digoxin and a few other cardiac glycosides, however, digitoxin seems most promising as an eventual anti-cancer drug. Considering the molecular modes of actions and pharmacokinetics of digitoxin; glioblastoma, pancreatic cancer, leukemia/lymphoma, kidney cancer, urothelial carcinoma and cholangiocarcinoma are some of the most interesting types of cancer for digitoxin treatment. Digitoxin can be combined with chemotherapy, immune therapy and radiotherapy in these clinical trials.

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