

METALS IN ONCOLOGY: AN OVERVIEW

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Abstract

This paper is an attempt to survey the literature of metal in oncology and also to give relative insight of effectiveness of different metals and their compounds against tumors cell lines. In this article I have summarized the anticancer activities of the certain active metals such as arsenic, tin, gallium, bismuth, and antimony. Arsenic is present in the anomaly of displaying anti-cancer and oncogenic properties simultaneously. Organic compounds of tin exhibit anti-cancer activity similar to cis-platin compound of platinum. The anti-proliferative effect of gallium could be related to its completion with iron atom. Bismuth directly affects Helicobacter pylori and gastric lymphoma: the effect of bismuth complexes of 6-mercaptopyrine are promising. Some antimony organic compounds show interesting result.

Keywords

Oncology, arsenic, tin, gallium, bismuth, antimony.

Introduction

The existence of relationship between cancer and metal is known to all oncologists. However, various aspects about these relationships are ignored by many. It is surprising to observe that metals are able to do the best and the worst. i.e. metals are able to induce cancer and to treat cancer. Some of them are even able to perform both, together with their organic derivative have been tested for their anti-proliferative activity. The toxicity as well as therapeutic value of organo metallic compounds of these elements is a continuing

area of research and a very brief survey being provided here for such elements and their derivatives.

Arsenic: Arsenic is well known for its acute toxicity but it carries also a terrible chronic toxicity. Since, it can induce cancer. Although it does not seem to be a mutagen in vivo, it interacts with DNA. Arsenic exposure in certain animals and in humans contributes to skin neoplasia by chronic stimulation of several growth factors.

It appears that arsenic acts at the level of tumours promotion by modulating the

signaling pathways responsible for cell growth and apoptosis. Arsenic induces chromosomal abnormalities and disruption of DNA methylation and of repair systems. Arsenic induced oxidative stress with subsequent DNA damage could explain the toxicity of arsenic. The actions of arsenic can eliminate transformed cells, which could protect organism from cancer and possibly could be its mechanism as arsenic and vanadium. Almost all metals are able to generate reactive Oxygen species (ROS), this property explains a great part of both their carcinogenicity and their aptitude to neat cancer. Oxygen is an absolute necessity for life and it is also worst carcinogenic molecule that we must endure during all over life time. This means that we must be careful to always manage a good reserve of intracellular reducing potential. Among the non platinum group metals, non transition metal and metalized, viz, Ga, Sn, As, Sb and bismuth along with selenium of action against tumour cells.

Tin: Because platinum and tin have common properties, for instance their possible oxidation states, tin compounds were screened as early as in 1980. The first organotin compounds, for which the antitumour properties were examined, were formally similar to cisplatin, or to its analogous carboplatin or paraplatin. They exhibit borderline activities against P-388 and L210 leukaemias *in vivo*. Arakawa studied the *in vivo* activity of di-n-butyltin dichloride towards Ehrlich ascities tumour, IMC carcinoma, P-388 lymphocytic leukemia and sarcoma 180 systems, and also showed that this compound influences of the DNA synthesis of proliferating cells. Many diorganotin compounds, R_2SnX_2 , were investigated in the content of their antitumour potential. The influence of the R groups and of the X ligands on the cavity was examined. (Gielen, 2002).

In 1986, Gielen group published a series of patents that initiated the search for antitumor active organotin compounds. Later on in a review, he presented an overview of his

research during the last 15 years. Some of these results have been reviewed before and much of this work has been potential. In recent review Gielen discussed the development of antitumour organotin derivatives for selected classes of compound such as tetraorgano dicarboxylatodistannoxones and related diorganotin dicarboxylates, and for tri organotin carboxylates. Among the carboxylate groups used are steroid carboxylates and other biologically relevant carboxylate. High to very high *in vitro* activities have been found, sometimes equaling that of doxorubicin. Solubility in water is an important issue, dominating the *in vivo* testing of compounds. Polar substitutes like fluorine or polyoxalkyl moities, improve the water solubility. Although organotin derivatives constitute a separate class of compounds, the comparison with cisplatin is in evitable. Among the observed toxicities, neurotoxicity, known from platinum cytostatics and gastrointestinal toxicity typical for many oncology drugs, have been detected, but to lower extent. Further research to develop novel useful organotin antitumour compounds needs to be carried out (Gielen, *et al.* 1992, Gielen 1994).

Gallium: Gallium is the second metal ion, after platinum, to be used in cancer treatment (Collery *et al.*, 2002). Its activities are numerous and various. It modifies three dimensional structure of DNA and inhibits synthesis, modulates protein synthesis, inhibits the activity of a number of enzymes such as ATPase, DNA polymerases, ribonucleotide reductase and tyrosine-specific protein phosphatase. Ga alters plasma membrane permeability and mitochondrial functions. Ga salts are taken up more efficiently and more specifically by tumor cells when orally administered. New compounds have been prepared. Gamaltolate, doxorubicin-Ga-transferring conjugate and Tris (8-quinolinoloto) Ga (III), which show interesting activities. Ga toxicity is well documented *in vitro* and *in vivo* in animals. In

humans, the oral administration Ga is less toxic and allows a chronic treatment, allowing an improvement of its bioavailability in tumours by comparison with the parenteral use. The anticancer activity of Ga salts has been demonstrated but other effects have also been noted such as many bone effects that could be useful in bone metastatic patients. It has also been shown that a long period of administration could induce tumour fibrosis Ga is synergistic with other anti cancer activity of Ga should not be ignored, but the schedule of administration still needs to be optimized and new compounds are now under clinical investigation.(Collery *et al.*, 1991).

Bismuth: In the medical field, bismuth compounds are used to relive diaper (nappy) rash, treat burns as well as to treat gastric disorders such as diarrhea. Importantly, bismuth compounds are effective against the bacterium; helicobacter pylori (abbreviated H.pylori) which causes peptic ulcers. Peptic ulcers are sores which are formed in the stomach wall or duodenum of the small intestine. Previously, it was thoughts that peptic ulcers were caused by eating spicy food or by stress.

However, in 1982, it was discovered that the bacterium, H.pylori, is responsible for peptic ulcers. H.pylori is a rod shaped, spiral bacterium. It weakens the protective mucous lining of the stomach and duodenum and thus allows the stomach acid to irritate the sensitive stomach wall. It is suspected that stomach cancer may also develop from the presence of H-pylori. Hence it is important to try and eradicate the bacteria. At present bismuth subcitrate and bismuth subsalicylate are used to treat such medical conditions, of which both are Bi (III) ions. Their empirical formulas are often given as $K_3(NH_4)[Bi_6O_3(OH)_5(Hcit)_4]$ and $OC_6H_4COOBio$ respectively. It has been hypothesised that the biological effects of Bi (III) are a result of their binding to DNA and proteins. However, there is still considerable debate on this issue (Tiekink, 2002, LiH, et al.

1997, Carraher *et al.* 1983 & Haiduc, *et al.* 1995).

The potential of bismuth as anti-cancer drugs has not been fully explored despite the use of bismuth in other medical applications. As some other organometallic compounds have been shown to be biologically active against human cancer cell lines, the possibility of bismuth compounds as anti-tumour drugs has been investigating. Studies of bismuth 6-mercaptopyrine and other thiolates have already shown some anti-tumor activity. $Bi(SR)_3$ has been shown to be more potent than platinum(II) analogue $[Pt(SR)_2]$ and at higher doses than the palladium (II) species.

Antimony: Despite their medicinal efficacy, the exploration of the antitumour potential of antimony compounds is not as well developed as for other metal containing species. The results of cytotoxicity and antitumour screening for antimony and antimony (V) compounds have been reviewed (Tiekink, 2002). The most studied antimony (III) compounds in the context of antitumour activity are organometallic in that they feature antimony to carbon bonds. Thus, a pair of diphenyl antimony (III) thiolates, i.e., $Ph_2Sb(S_2PPh_2)$ and $Ph_2Sb(S_2POPr)_2$ have been investigated. Early work on these and related compounds both *in vitro* and *in vivo*, showed that compounds containing antimony (III) were more active than their organotin congeners and that $Ph_2SbS_2P(OPr)_2$ was more active than $Ph_2Sb(S_2PPh_2)$ against Ehrlich ascites tumour. The *in vivo* screening against P-388 leukaemia in mice has been investigated. Three of the four antimony (III) compounds were found to have marginal activity (Tic<125%) and definitely not as active as the widely employed anti-cancer drug cis-platin, i.e., $(NH_3)_2PtCl_2$, in this model. Compound $Ph_2SbS_2P(OPr)_2$ was the most active but increased doses were associated with increased toxicity. A Subsequent studies showed that both $Ph_2Sb(S_2PPh_2)$ and $Ph_2SbS_2P(OPr)_2$ and mutagenic potential with $Ph_2SbS_2P(OPr)_2$ having the higher effect. (Tiekink, 2002). Sodium stibogluconate

(SSG) appears to be a better inhibitor than suramin which is compound known for its antineoplastic activity against several types of cancer (Cabrera, *et al.*, 2008).

Two reports are available on the cytotoxicity of antimony (V) compounds (Carragher *et al.*, 1983, Haiduc, 1995). In the first report the potential inhibitory effects of series triphenyl antimony (V) polyamines were described. The results of this study show that all compounds displayed some inhibition and the assay showed that, generally, increased inhibition was associated with increased doses. The most potent compounds across the series of three cell lines (BHK-21 baby hamster kidney, L929 mouse connective tissue and HeLa human epitheloid carcinoma) were those containing the dianions derived from adenine (H_2NR^2) and 2,6-diaminoanthraquinone (H_2HR^7). Selectivity against the BHK-21 cell line compared with the other cell lines was exhibited by the compound containing the dianion derived from 2,4-diamino-5-(3,4-dimethoxybenzil) pyrimidine (H_2NR^6).

The second report of antimony(V) compounds studied for cytotoxicity described monomeric species of the general formula $R_3Sb(OCC_6H_3-2-OH-S-Y)_2$ where R=Me or Ph and Y=H Me

or OMe. Screening against a variety of human tumour cell lines showed that these species had no significant activity and their study was not pursued (Haiduc, *et al.*, 1995).

Experimental

In-vitro Antitumour Testing: The cell proliferation activity of the compounds was measured by using MTT method. Measurement of cell viability and proliferation forms the basis for numerous *in vitro* assays of all populations' response to external factors. The reduction of tetrazoleum salts is now widely accepted as a reliable ways to examine the cell proliferation activity.

The yellow coloured tetrazoleum MTT (3-(4,5) dimethyltetrazoyl-2)-2,5-diphenyl tetrazoleum bromide) is reduced by metabolically active cell line; by the action of dehydrogenase enzymes; to generate reducing equivalent such as NADH and NADPH. The resulting purple color can be solubilised and quantified by spectrophotometer method.

Results and Discussion

The antitumour screening result of Ar_3SbL_2 ($Ar=C_6F_5$, C_6H_5 , $p-CH_3C_6H_4$; $L=NR_2$, $OCOR$) are presented in Table 1.

Table 1
IN-VITRO ANTITUMOUR ACTIVITY OF TRIARYL ANTIMONY(V) DERIVATIVES

S.No.	Compounds	Cell No. '10 ⁴	Activity
1.	$(C_6F_5)_3Sb(-\overline{NCOCH_2CH_2CO})_2$	9.45 ± 0.65	+
2.	$(C_6F_5)_3Sb(-\overline{NCOCH_6H_4CO})_2$	2.29 ± 0.82	+
3.	$(C_6F_5)_3Sb(-\overline{NCOCOC_6H_4})_2$	9.75 ± 0.42	+
4.	$(C_6F_5)_3Sb(-\overline{NC(CH_2CL)NC_6H_4})_2$	8.15 ± 0.91	+
5.	$(C_6H_5)_3Sb(OCOCH_2NHCO_6H_5)_2$	11.89 ± 1.15	-
6.	$(p\text{-tolyl})_3Sb(OCO(OH)_3C_6H_5)_2$	11.76 ± 1.10	-
7.	$(C_6H_5)_3Sb(OCOC_6H_5)_2$	13.24 ± 1.16	-
8.	$(p\text{-tolyl})_3Sb(OCO(OH)C_6H_5)_2$	12.15 ± 1.15	-
9.	Positive control	40.26 ± 3.23	-
10.	Negative control	10.21 ± 1.01	-

In-Vitro Antitumour Activity: The antitumour screening result indicates that compounds with fluorophenyl ring and imide moities viz, succinimide, phthalimide, isatin show positive *in vitro* antitumour activity against human breast adenocarcinoma cell lines (MCF-7). Whereas compounds with phenyl and carboxylate moities are found in active against MCF-7. So, in general, presence of fluoro and amide group are most

desirable for better antitumour activity of antimony (v) derivatives.

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