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2,4 - DINITROBENZOTHIAZINE AS AN ANTI-CANCER DRUG

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ABSTRACT: 2,4 - dinitrobenzothiazine possesses broad spectrum biological activities such as anticancer, antioxidant, anti-inflammatory, anti-tumour, antiviral, antibacterial, anti-proliferative, anti-diabetic, anti-convulsant, analgesic, anti-tubercular, antimalarial, anti-leishmanial, anti-histaminic and anti-fungal among others. The BTA scaffolds showed a crucial role in the inhibition of the metalloenzyme carbonic anhydrase (CA). In this review an extensive literature survey over the last decade discloses the role of BTA derivatives mainly as anticancer agents. Such compounds are effective against various types of cancer cell lines through a multitude of mechanisms, some of which are poorly studied or understood. The inhibition of tumour associated CAs by BTA derivatives is on the other hand better investigated and such compounds may serve as anticancer leads for the development of agents effective against hypoxic tumours.

KEYWORDS: 2,4-dinitrobenzothiazine, anticancer, tumour inhibitor, hypoxic, broad spectrum, biological

I. INTRODUCTION

It is a fused benzoheterocycle¹ which is present in many naturally occurring products and is responsible for the medicinal, pharmacological and pharmaceutical applications of such natural products. It exhibits remarkable and prevalent biological and pharmacological activities against different types of tumours and cancer cell lines such as HeLa (human cervical cancer cell line), SW480 (human colon adenocarcinoma cell line), HepG2 (human liver carcinoma cells)¹⁶, mammary and ovarian tumour cell lines¹⁷, colon, nonsmall-cell lung and breast subpanels cell lines¹⁸, and HCC (hepatocellular carcinoma)¹⁹ etc. Cancer is the most prominent, notably complex and lethal disease which became a serious concern of today's medical science. It poses a great challenge to medical scientific community for development of drugs, medicines and procedures for safer treatment and cure of cancer disease²⁰. These neoplasm tumour cells are diversified, heterogeneous cells with rapid proliferative properties. These neoplasm malignant tumours, have potential to invade or spread to other parts of body through blood stream and lymphatic system. The chemical 2,4 - dinitrobenzothiazine² and screened for cytotoxic activities against two human cell lines U-937 (human macrophage cell line), THP-1 (human leukaemia monocytic cell line) and B16-F10 (mouse melanoma cell line). It is encouraging for the development of new anti-cancer therapeutic agents and this will be good addition in armamentarium that consists of paclitaxel, cisplatin and doxorubicin drugs.³

Cancer is very dangerous disease with uncontrolled growth and rapid spreading of abnormal cells⁶. Several external and internal factors are caused to abnormal growth of cell lines and induced the different cancers.⁴ Currently, three types of treatment are available for cancer disease including chemotherapy, radiotherapy, and surgery.⁵ The standard treatment for cancer patients is chemotherapy, in which different chemotherapeutic agents are used to kill the cancer cells without any harmful effective on normal kidney cells. Nitrogen atoms contain heterocyclic ring moieties that are present both in natural products and in synthetic derivatives and exhibited potent anticancer activities against different human cancer cell lines. The decision to use a certain anticancer drug depends on many factors, including the type and location of the cancer, its severity, whether surgery or radiation therapy can or should be used, and the side effects associated with the drug.⁷ Most anticancer drugs are administered intravenously; however, some can be taken orally, and others can be injected intramuscularly or intrathecally (within the spinal cord). The treatment of cancer is complicated in that the drugs used target human cells, albeit cells that have undergone genetic changes and are dividing at a fast and uncontrolled rate. However, certain anticancer drugs can differentiate to some degree between normal tissue cells and cancer cells, and the rate at which cancer cells proliferate may in fact play a role in the apparent selectivity of agents.⁸

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For instance, alkylating agents, which act on cells at all stages of the cell cycle, appear to be most toxic to cells in the synthesis, or S, stage, when DNA is in the process of replicating and unpaired nucleotides (the nitrogen-containing units of DNA and RNA) are most vulnerable to alkylation (the addition of an alkyl group). In the late 20th and early 21st centuries, the identification of molecular features unique to cancer cells fueled the development of targeted cancer therapies⁹, which possess a relatively high degree of specificity for cancer cells.

II.DISCUSSION

The specificity of these anticancer drugs plays an important role in reducing the severity of side effects associated with the drugs' use. Indeed, because cancer cells are similar to normal human cells, anticancer agents are generally toxic to normal cells and can cause numerous side effects, some of which are life-threatening. Such side effects include hair loss, sores in the mouth and on other mucous membranes, cardiac anomalies, bone marrow toxicity, and severe nausea and vomiting¹⁰. The bone marrow toxicities result in anemia as well as in decreased resistance to infectious agents. Permanent infertility can also result. Those adverse effects may require that the drug dosage be reduced or the drug regimen be changed to make the drug tolerable to the patient.¹¹

In rare instances prolonged use of anticancer drugs of 2,4 - dinitrobenzothiazine can lead to the development of secondary cancers. The type of agent, the primary cancer that it is used to treat, and the total cumulative dose administered¹² influence the extent to which an anticancer drug is carcinogenic (cancer-causing). Frequently occurring secondary cancers associated with anticancer drug therapy are myelodysplastic syndrome and acute leukemias, risk of which is increased particularly with the use of alkylating agents and topoisomerase inhibitors (e.g., etoposide). The side effects associated with anticancer drugs can be reduced through the use of multiple agents, which often enables the administration of lower dosages of each drug. The use of multiple agents may also reduce the incidence of cellular resistance, a phenomenon that allows tumours to escape treatment and to continue to grow after a period of remission (absence of disease activity). Multidrug therapy is based on the premise that different types of anticancer drugs exert their effects in a certain part of the cell cycle (e.g., cell growth phase, cell division phase, resting phase).¹³ Thus, one drug may be used to stop the growth of cancer cells in a certain phase, while another agent may work at a different phase. In addition to using complex regimens that employ several drugs, cancer chemotherapy is often combined with surgery to reduce the number of cancer cells and with radiation treatment to destroy more cells.¹⁴

Cancer treatment options include surgery, radiation and chemotherapy, or a combination of them. Chemotherapy is a systemic approach and consists of administering one or more chemicals that can damage fast-growing cells, such as cancerous ones. However, these agents, being non-selective, usually damage healthy cells and tissues with rapid turnover, causing severe toxic effects. The rapid emergence of drug resistance, the instability of the molecules and the poor solubility in water, which makes them unable to permeate through cell membranes, represent further drawbacks of chemotherapy.¹⁵ To overcome these limitations, two or more chemotherapeutics are usually used in combination. Other therapeutic strategies to treat different types of cancer are based on the use of small molecules, including genes, small RNAs and plasmids, which, however, show limitations due to their poor stability in vivo.¹⁶

III.RESULTS

Light degradation of anticancer drugs frequently results in transformation products that are also responsible for toxic effects. The photodegradation of cyclophosphamide and iposphamide has been investigated using ruthenium-doped titanate nanowires in distilled water and wastewater under UV-vis irradiation.¹⁷ Dacarbazine, an alkylating agent commonly used in combination with these chemotherapeutic agents for the treatment of metastatic malignant melanomas, Hodgkin's lymphoma and pheochromocytomas, is converted by light into 4-diazoimidazole-5-carboxamide. This photo-transformation product is often responsible for the pain reactions observed during peripheral intravenous infusion during clinical application.¹⁸ The photodegradation profile of the drug solutions was determined using HPLC coupled to UV detection. The study demonstrated that photoproduct production increases in a time-dependent manner up to 4 h at 4 and 25 °C despite the sample being light-shielded, suggesting that light shielding is not

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required in sample preparation. The development and application of vesicular systems capable of ensuring controlled delivery of anticancer drugs to the desired site of therapeutic action in adequate quantities to exert their actions are increasing. These systems improve therapeutic efficacy while reducing negative side effects,¹⁹ providing many advantages, including improved pharmacodynamic and pharmacokinetic profiles, which result in a prolonged half-life and enhanced drug stability, ensuring protection from chemical or physical degradation. Since most antineoplastic agents are very sensitive to different conditions, in clinical practice, improvement in the drug stability profile can simplify the work of pharmacists during the preparation of different formulations, and of healthcare professionals when handling the drugs that need to be administered in hospital care²⁰. Furthermore, improving the stability of anticancer agents could facilitate home therapy as the drugs could be supplied to patients via portable elastomeric pumps without risking their alteration and, therefore, treatment failure.²¹

The currently available nanocarriers for anticancer drugs vary in structures, sizes and physicochemical properties. These systems can be of natural origin, and, therefore, made up of simple structures derived from phospholipids, such as lecithin, and of synthetic nature and thus characterized by more complex structures consisting of polymers sometimes complexed with metals. Niosomes (non-ionic surfactant vesicles)²² are one of the most commonly applied carriers for anticancer drugs. These vesicles are obtained by the hydration procedure of a non-ionic surfactant with cholesterol in which the surfactants form a closed bilayer vesicle in an aqueous medium based on its amphiphilic nature. In this structure, the surfactant molecules are oriented away from the solvent so that the hydrophilic ends of the non-ionic surfactant point outwards and the hydrophobic ends face each other to form the bilayer,²³ whereas the hydrophilic heads remain in contact with the aqueous solvent. As for the natural liposomes, the properties of the niosomes depend on the composition of the vesicles, size, lamellarity, tapped volume, surface charge and concentration. However, unlike niosomes, liposomes are expensive, and their components, such as phospholipids, easily suffer oxidative degradation. This behavior requires special storage conditions and makes liposomes challenging to handle. All these structures include both aqueous compartments for the incorporation of hydrophilic molecules and lipid layers for the transport of lipophilic molecules²⁴.

IV. CONCLUSIONS

Over the last few decades, the use of nanoparticle (NP)-based DDS of 2,4 - dinitrobenzothiazine has shown numerous advantages in cancer treatment, including the ability to overcome drug resistance caused by overexpression of drug efflux transporters,²⁵ defective apoptotic pathways and a hypoxic environment. For example, NPs can avoid the exposure of anticancer drugs to efflux transporters as they enter the cell primarily through endocytosis rather than diffusion. Usually, the type of NPs used in cancer therapy (organic, inorganic or hybrid) is designed or chosen based on their size and characteristics, as well as the pathophysiology of the tumors. Organic NPs include liposome- and polymer-based NPs,²⁶ such as micelles and dendrimers, whereas inorganic NPs include gold NPs (Au-NPs), carbon nanotubes, silica NPs, magnetic NPs and quantum dots; finally, the hybrid NPs that combine the advantages of the different types include the lipid-polymer, organic-inorganic hybrid NPs and cell-membrane-coated NPs.^{27,28}

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