# Elesclomol: A study on copper induced melanoma treatment

**Harshini Raja[1], P. Vishnu[1],C. Pavani[1], N. Sadhana[1], B. Sunitha Kumari[2], G. Jyothi[1]***

[1]Department of Pharmaceutical Engineering, B V Raju institute of Technology, Narsapur, Medak Dist, Hyderabad, Telangana, India, 502313.

[2]TKR College of Pharmacy, Meerpet, Hyderabad, Telangana.

Email: jyothi.g@bvrit.ac.in

**Abstract**

Elesclomol is a novel anti-cancer drug that triggers apoptosis in cancer cells. It has been designated as a fast-track drug and an orphan drug by the United States Food and Drug Administration (USFDA). Elesclomol was seen to induce oxidative stress but now it is famous for its anti-cancer properties. The anti-cancer activity based on the proliferation of cancer on the mitochondrial membrane. Elesclomol induces cuproptosis which is a process of cell death due to accumulation of copper in the mitochondrial membrane.

**Keywords:** Elesclomol, Metastatic melanoma, Cuproptosis

## 1. Introduction

Elesclomol is a drug formulated by Synta Pharmaceuticals, initially for the treatment of malignant melanoma, later a chemotherapeutic adjuvant. Cancer cells preferentially produce energy through glycosis even in the presence of oxygen, although further studies have shown its link to proliferation of cancer cells in the mitochondrial membrane. This can damage the integrity, structure and the membrane potential of mitochondria leading to apoptosis and altered energy production. The anti-cancer property of Elesclomol was earlier recognised for its ability to accumulate oxidative species to induce oxidative stress ranging from the cell bounds, the mitochondrial membrane and DNA contents. Meanwhile, the property relies on its ability to move copper ions to induce cuproptosis. Copper is a trace element in the body and the accumulation of cupric ions can lead to cytotoxic situations by reactions between copper ions and proteins (1-3).

## 2. Melanoma

Melanoma is a type of skin cancer that develops due to pigment producing cells called melanocytes. The mechanism of melanoma involves mutations in the DNA of melanocytes due to Ultraviolet radiation exposure. This can cause disruptions in cell DNA and lead to uncontrolled growth and become cancerous cells. Lesions and moles on the surface of skin indicate tumors. Melanoma is also based on genetic inheritance and lifestyle disorders. There are two types of melanoma cancers – Benign and Malignant (Metastatic). Most tumors tend to be benign in skin cancers such as moles whereas the malignant cancers spread to various body parts through the process of metastasis. About 1 in 10 individuals get affected by metastatic melanoma, making it an uncommon disease. Patients with metastatic melanoma survive for a median of 8.5 months. Treatment often includes close observation, subjecting to chemotherapeutic agents like dacarbazine that shows a response rate of 15% to 20% is widely used. Dacarbazine is commonly used to treat cancers such as melanoma, Hodgkin's lymphoma and soft tissue sarcomas. It works as an alkylating agent that adds an alkyl group to the DNA chains, thus disrupting the genetic structure and preventing cancer cells from multiplying. Furthermore, it induced cell apoptosis by targeting rapidly dividing cells. Dacarbazine is generally administered intravenously but oral form such as Temozolomide is also used and shows a response rate of 20%. Temozolomide is recognised for its ability to penetrate the Blood Brain Barrier (BBB) and effects on central nervous system. Either of the drugs are always administered in a combination. Additionally, combination drugs such as cisplatin, carmustine, paclitaxel and docetaxel are administered. This led to introduction of combination chemotherapy including tamoxifen. Although it initially showed high response states, it was concluded that the presence of tamoxifen showed no greater change in responses. This led to studies pertaining to immunotherapy and bio chemotherapy to cytotoxic cell death studies for treatment of metastatic melanoma in patients. Furthermore, cell apoptosis using platinum and copper mediated ions was a subject that soon rose to interest amongst scientists. The use of accumulation of trace elements in the body leading to toxicity and expulsion of cancerous cells (4).

## 3. Pharmacokinetics

Elesclomol is administered intravenously, leading to rapid and complete bioavailability into systemic circulation. Elesclomol binds with cupric ions and form a permeable complex which upon entering the mitochondrial matrix reduces into cuprous oxide in the presence of the protein mitochondrial ferrodoxin I. Cuprous oxide ions can generate reactive oxygen species (ROS) via Fenton reaction. In this reaction, Cuprous oxide ions react with hydrogen peroxide to give hydroxyl radicals which are highly reactive ROS. They play a complex role in cancer cells as they are essential at low levels but high levels can cause damage to cellular components. Cuprous ions are also essential in metalation of cytochrome in the mitochondria. This occurs by reaction of metal cuprous ion into cytochrome proteins is crucial for electron transport chain in cellular respiration. In addition to that, they are required for the maturation of cuproenzymes, which refer to enzymes containing copper as a cofactor. During maturation, the copper ions are incorporated into the active site and participate in catalytic processes. Ceruloplasmin, another cuproenzyme metabolised primarily for iron metabolism of the body. Elesclomol undergoes hepatic metabolism and glomerular filtration in process of excretion (5).

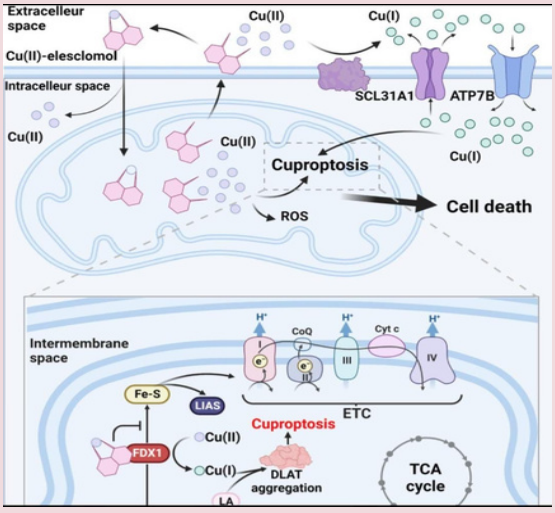


**Figure 1. Cuproptosis mechanism**

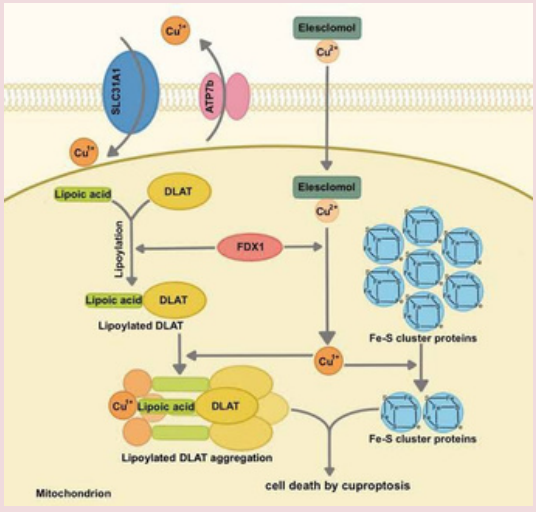


**Figure 2. Copper pyrazole anti-cancer activity**

## 4. Pharmacodynamics

Elesclomol biological effects revolve around inducing oxidative stress in cancer cells leading to mitochondrial dysfunction, affecting catalytic reactions, inhibiting angiogenesis, the process of formation of new blood vessels for metastasis, ultimately leading to apoptosis. Elesclomol in the bloodstream reacts with proteins such as Human Serum Albumin to serve as a carrier agent for distribution and availability in the body. Elesclomol interaction with the central nervous system, primarily the brain is very limited due to the poor blood brain barrier penetration of the drug. The drug interacts with the liver where it is subjected to hepatic metabolism and is converted to metabolites for excretion. Kidneys via glomerular filtration excrete the drug through urine. The dosages of Elesclomol varied as it is patient specific and ranges from 100 – 213 mg/m^2 in a treatment schedule every 3 weeks. The bioavailability of the drug administered through intravenous route is considered to be 100% as it directly enters bloodstream bypassing first pass metabolism (6).

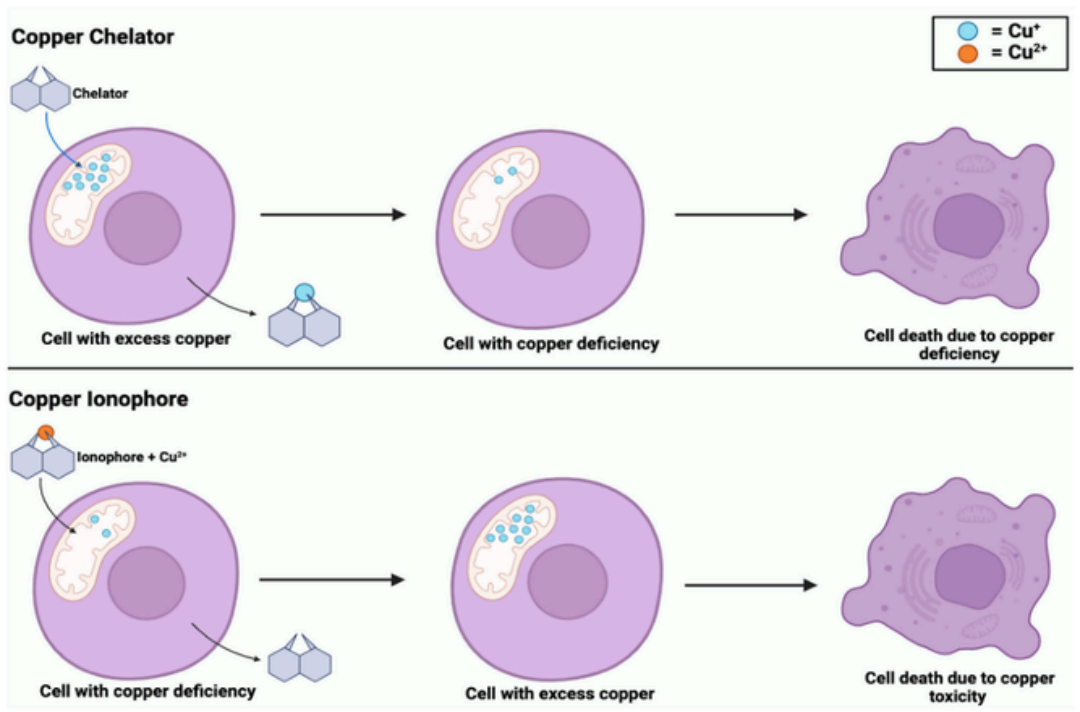


**Figure 3. Cytotoxic death due to copper ions**

## 5.Clinical trials and orphan designation

In preclinical models, the drug showed synergic bond with paclitaxel and docetaxel. In phase 1 study, the results obtained were partial response when patient was subjected to paclitaxel, intraperitoneal cisplatin, a sargramostim tumour vaccine, trabectedin, and liposomal doxorubicin. There were no recorded adverse side effects. 1,500 subjects had enrolled in clinical trials, and more than 600 subjects have received elesclomol as a single agent, or in combination with paclitaxel or docetaxel. More than 500 subjects were administered the elesclomol/paclitaxel combination at or above a dose of 213 mg/m2 given weekly for 3 weeks of a 4-week cycle. A phase 3 trial encompassing patients administered with 213 mg/m^2 of Elesclomol with 80 mg/m^2. The study was shortly terminated and abandoned as this dosage led to patient deaths and the risks of such and adverse reactions had no specific patterns. Shortly after, Elesclomol received orphan drug designation primarily as it was developed to treat rare cancer conditions like melanoma.

Orphan drug designation is granted by regulatory agencies like FDA for drugs intended for treatment, diagnosis and prevention of rare diseases that affect a small number of people. Drug developers receive numerous benefits from the agencies to encourage the treatments for rare diseases that have unmet medical needs (7-9).

### 5.1 Orphan designation

The Orphan Designation Act (1983) of United States was initiated to encourage finding treatments of rare diseases. Around that decade, treatments of such diseases rarely existed and was often overlooked. Current status, inclusive of low R and D cost allocation, orphan designated drugs and diseases are one of the most expensive and profitable businesses. The definition of the work orphan drug was on the basis of not just how rare the disease was, but the rarity causing it to be neglected in the market overall. In 1984, The Food and Drug Administration (FDA) redefined orphan drug as rare diseases that affect less than 200,000 people in the United States. Research supports that orphan drug studies are more profitable than non-orphan drugs as of today (10).

## 6. Conclusion

Metastatic melanoma is a rare disease that affects less than 200,000 people a year, the studies for which constitute orphan and rare designated drugs. It is a novel drug that induces oxidative stress by accumulation of copper ions in the mitochondrial membrane of the cancer cells. Cuproptosis refers to cell death due to accumulation of copper ions in a matrix. This is caused by conversion of cuprous oxide ions into cupric ions. Cupric ions lead to damage in cell wall upon contact and lack of, and increase of these ions are harmful to the cancer cells. Elesclomol is an orphan designated drug used with the combination of paclitaxel and docetaxel for treatment of metastasis melanoma. Dosage and combinations of Elesclomol in phase three trails did not lead to increase in patient mortality causing it to be subjected to further investigation and clinical trials and awarding of orphan status by the Food and Drug Administration. Orphan drug studies are quite profitable and rewarding in terms of R and D. Further research into cuproptosis and Elesclomol interactions could uncover novel understanding and promising therapeutics aimed at treating melanoma (1).

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