The use of metals as a treatment for cancer

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Introduction

Cancer is the transformation and uncontrolled growth of cells in the body. This is facilitated by a series of genetic mutations that allow the cancer cells to escape the body's surveillance system, multiply unchecked and progressively increase the size of the tumor until it eventually metastasizes. One of the earliest forms of treatment was the use of small chemicals to kill the tumor cells. Such "chemotherapies" have been accepted as a distinct class of treatment modality designed to inhibit the rapid proliferation of malignant cells. Many of these chemotherapies accomplish this by interacting with and damaging the cancer's DNA. Once this damage occurs, the cancer cell can temporarily pause its multiplication to repair the DNA. Ideally, this repair fails, and the cancer dies from the treatment.

The Central Dogma of metal-based therapy

While chemotherapies, as a class, are accepted to prevent the growth of rapidly proliferating cells, many small chemicals in this class do so in very different ways. The most common sub-class of chemotherapy is metal-based platinum therapy. This type of therapy is very common in that 50% of all chemotherapy patients receive some type of a platinum-based treatment regimen. Currently, there are three FDA approved platinum-based drugs: 1) cisplatin, 2) carboplatin and 3) oxaliplatin.

Of the three, cisplatin is the most widespread and commonly used as front-line therapy alone or in combination with other therapeutic agents or modalities to treat testicular, ovarian, cervical, breast, bladder, head and neck, esophageal, lung, mesothelioma, brain and neuroblastoma cancers. While almost universally curative for testicular cancer, cisplatin has historically been a problematic therapy due to its toxic nature. Originally discovered in 1845, its therapeutic potential was discovered much later in 1965 and eventually authorized for medical use in 1978. A major clinical hurdle for its use was the onset of severe and irreversible nephrotoxicity, which almost halted the drug's clinical development. However, a pre-hydration diuretic regimen designed by Dr. Irwin Krakoff and his clinical team increased drug excretion through the kidney, reduced kidney damage, and allowed cisplatin to become clinically established.[1]

Carboplatin was approved in 1987 as a second-generation version of cisplatin. While its method of attacking the cancer is similar to cisplatin, it possessed properties that allowed direct infusion rather than the required pre-requisite kidney hydration for cisplatin. In addition, carboplatin was found to have less severe side effects relative to cisplatin. However, carboplatin does induce loss in blood cells, such as platelets (thrombocytopenia) and white blood cells (leukopenia). To date, carboplatin has become the "clinician's choice" over cisplatin for use against most of the cancers.

Finally, oxaliplatin was approved in the US in 2002 for the treatment of colorectal cancer as part of the chemotherapy combination FOLFOX. While found to be associated with less toxic side effects, patients treated with oxaliplatin were found to suffer from neurotoxicity, in particular peripheral neuropathy, which is a persistent tingling numbness in the hands and feet. While originally accepted that oxaliplatin's anticancer effects were similar to cisplatin and carboplatin (e.g., DNA damage), recent data and research has proposed oxaliplatin to have a different mode of anti-tumor activity, with targeting of the cancer cell ribosome as the main mechanism.[2]

When platinum treatment doesn't work: Platinum Resistance.
Cisplatin is credited with increasing the cure rate in testicular cancer from 10% to 90%. However, its utility in the treatment of other cancers is limited due to intrinsic or acquired platinum drug resistance. This is evident in low 5-year survival rates of non-small cell lung, mesothelioma and ovarian cancers in the range 5-35.

There is a significant amount of research surrounding drug resistance. To date, it is accepted that there are multiple functional defects in the cancer that lead to resistance. However, the most formidable is the operational loss of the tumor suppressor protein p53. Normally, the p53 protein is heavily controlled and present in an inactive state in normal and cancer tissues. Chemotherapy induces its activation through chemical modification, such as phosphorylation, that enables p53 to kill tumor cells as a therapeutic response. However, in cancer cells, selection pressures prevent p53 from becoming activated, through either loss of the chemical modification process or its own mutation. This inactivation leads to increased survival of cancer cells. Other mechanisms of resistance are also often found to co-exist within tumor cells.

However, it has been found that the cumulative effect of multiple mechanisms of platinum resistance can lead up to a 30-fold increase in resistance. In other words, a resistant cancer would need a 30-times greater dose of treatment to get the same response as a sensitive cancer. Such a dose, however, would be lethal in cancer patients.

Seems like platinums don't work well as a cancer treatment. Why do we keep using them?
While there are a multitude of more contemporary therapies available since the approval of cisplatin in 1978, platinums continue to maintain their frontline status due to their substantial effectiveness. However, these treatments become problematic when resistance is observed and the platinums lose their efficacy. As illustrated by Dr. Robert Ozols in 1985, some patients with tumors defined as clinically resistant responded to a high-dose cisplatin regimen.[3] In other words, the anticancer effects of platinum can increase at higher doses in patients that had recurrent disease or previously stopped responding to platinum combination therapy. However, outside of a clinical trial setting, this is not practical due to the dose-limiting toxicity of cisplatin.

What can we learn from all this?
Nature has inspired generations of scientists of all disciplines to accept that metals are essential for normal biological function. Living systems rely on metals to accomplish functions that are not possible otherwise. For example, iron is needed to effectively deliver oxygen from our lungs to all parts of the body. Other metals are essential in counteracting oxidants (i.e. acting as antioxidants) and in metabolism. Fields of interdisciplinary science and medicine have come to appreciate that metals have diverse function when modified correctly to achieve a specific goal.

With this in mind, significant medical research is devoted to better understand how metals can be chemically modified to elicit unique anticancer mode of actions that other treatment modalities cannot. For example, scientists and inventors of technology being developed by

InnovoTEX have found that metals, if designed correctly, can circumvent p53 resistance[4] and induce an anticancer immune response.[5]

InnovoTEX is developing an innovative platform technology based on texaphyrin-metal drug conjugates that are well-localized to tumor cells, highly effective, MRI-detectable, and less toxic than traditional chemotherapy. Platform candidates are in development for multiple solid tumor indications. Lead candidate, OxaliTEX, is a unique platinum-based drug designed for increased tumor drug uptake and to restore p53 activation in order to target platinum-resistant ovarian cancer in patients.

Further Reading

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