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Clinical Applications of a Combination Chemotherapy Using 8-Chloro cAMP and 8-Chloro Adenosine

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Clinical Applications of a Combination Therapy using 8-Cl cAMP and 8-Cl Adenosine

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Introduction

Dr. Cho-Chung from NIH first thought to use halogenated cAMP derivatives as competitive inhibitors of cAMP to slow down cancer cell mitosis (1). Experimental results indicated that 8-Iodo cAMP did not have any biological activity, while 8-Bromo cAMP showed minimum inhibition, and 8-Chloro cAMP (8-Cl-cAMP) provided significant anti-cancer activity.

8-Cl cAMP was found to be a broad spectrum anti-cancer drug against many cancer cells *in vitro* - such as in leukemia, breast cancer, lung cancer, etc. This molecule helped to slow down cancer cell growth giving time for the cancer cells to respond to signals from surrounding normal cells. This gave white blood cells sufficient time to recognize and eliminate the cancerous cells. Additionally, some of the cancer cells were observed reverting back to normal cells morphologically.

With its many positive results, 8-Cl cAMP entered Phase II clinical trials. However, the phosphate group on the 8-Cl cAMP made it very water soluble; consequently, it quickly flushed out of the patients' body, as do hydrophilic vitamins such as Vitamin C. Peristaltic pumps were thus employed to pump the 8-Cl cAMP into patients' veins continuously to maintain drug concentrations. Although 8-Cl-cAMP had very low human toxicity, high exposures to this drug resulted in side effects that prevented it from reaching Phase III clinical trials.

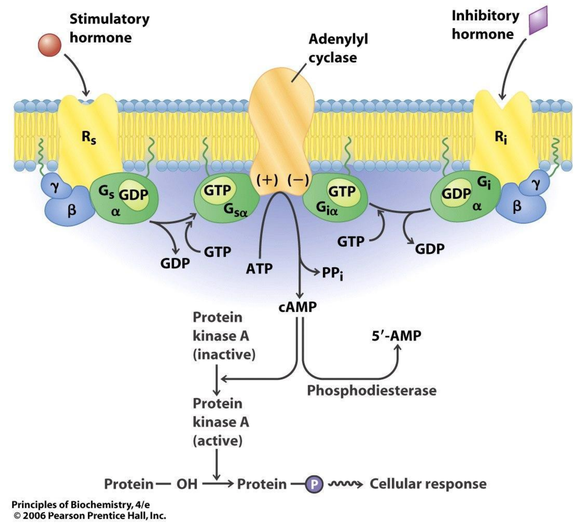
Since Adenosine can be converted to cAMP *in vivo* through the human biological pathway naturally, 8-Cl cAMP therefore can also be converted from 8-Cl-Adenosine through the same biological pathway. This has been confirmed by many published studies. Thus 8 Cl-Adenosine can serve as a pro-drug for 8-Cl-cAMP to provide a constant concentration of 8-Cl-cAMP in the cancer patient blood plasma. This can also reduce the dosage necessary for treatment. The combination therapy using 8-Cl cAMP and 8-Cl Adenosine (as a pro-drug of 8-Cl cAMP) will certainly provide the optimum clinical outcomes for cancer patients.

Discussion

Cyclic adenosine mono phosphate (cAMP) is a major component of various pathways which regulate cell growth and proliferation among other functions. The pathway begins with a membrane bound receptor that usually binds an endocrine hormone. The receptor is bound to a transmembrane protein that, once activated, stimulates a stimulatory or inhibitory trimeric G-protein, a guanine nucleotide-binding protein that acts as a switch inside cells to transmit signals that are received outside of the cell. The G-protein stimulates adenylate cyclase to cause the cyclization of ATP to cAMP. cAMP stimulates protein kinase A (PKA), which will convert ATP to AMP to phosphorylate other proteins. PKA will also phosphorylate the transcription factor cAMP Responsive Element Binding Protein (CREB). Once CREB is phosphorylated, it is activated and diffuses inside the nucleus where it interacts with DNA as a transcription factor, causing the transcription of certain genes.

8-Cl-cAMP and 8-Cl-Adenosine are both under clinical trials for their therapeutic effects in treating various types of cancer. These trials have met many issues, one of the major problems is their solubility properties. 8-Cl-cAMP is known to have high water solubility similar to that of vitamin C, thus the drug is not able to maintain high enough concentrations in the body to illicit a response before it is excreted. This problem was overcome by increasing the dosage given to patients which caused toxic side effects. These side effects can be mitigated, however, by what has been proposed here. Keeping in mind the solubility of 8-Cl-Adenosine and the fact that it is readily converted to 8-Cl-ATP which can be further converted to 8-Cl-cAMP through human biological pathways, a dosage of 8-Cl-Adenosine dissolved in human serum albumin could provide a constant 8-Cl-cAMP concentration in the blood serum for anti-cancer treatment.

Lowering the dosage of 8-Cl-cAMP and adding an IV dosage of 8-Cl-Adenosine would not only provide patients with the enhanced anti-cancer effects but also give the body a less toxic source of 8-Cl-cAMP in the form of 8-Cl-Adenosine. While this modification requires additional clinical research, augmenting 8-Cl-cAMP treatment with 8-Cl-Adenosine can give patients the more clinical benefits with minimum toxicity.



The Role of cAMP in Signal Transduction

Background

Both 8-Cl-Adenosine and 8-Cl- cAMP have been found to inhibit proliferation of cancerous cells. 8-Adenosine is under clinical phase I study at the M.D. Anderson Cancer Center under Dr. William Wierda for the treatment of chronic lymphocytic leukemia while 8-Cl-cAMP has advanced to clinical phase II studies. Within cells, 8-Cl-Adenosine and 8-Cl-cAMP are inter-convertible and can serve as pro-drugs for each other. The mechanisms through which 8-Cl-cAMP demonstrated the anti-proliferative effects have been studied and published. Findings by Simona Lucchi et al, (2) indicate that 8-Cl-cAMP is more effective in inhibiting cancer cell growth than the other PKA I-selective analogs. In this specific investigation, the use of 8-Cl-cAMP was associated with cell apoptosis, whereas the use of PKA I-selective analogs only inhibited cell growth. During inhibition of the p-38 MAPK pathway, the pro-apoptotic effect of 8-Cl-cAMP was prevented. Further studies suggested that the 8-Cl-cAMP and PKA I-selective analogs acted through these mechanisms; cell growth arrest is induced in cells carrying the BRAF-1 oncogene in the presence of PKA I-selective analogs, and 8-Cl-cAMP induced apoptosis through the p-38 MAPK pathway. These findings indicate that 8-Cl-cAMP indeed produces anti-cancer effects by slowing down cancer cell growth and inducing apoptosis for cancer cells. Thus 8-Cl-Adenosine, as a pro-drug of 8-Cl-cAMP ensures a sustained concentration of 8-Cl-cAMP in the blood plasma. The synergistic effect of using 8-Cl-cAMP and 8-Cl-Adenosine in multidrug combination therapy for cancer patients will maximize the clinical efficacy and duration of the anti-cancer effects.

Summary of Clinical Trials

- **The information toxicity and side effects of 8-Cl-cAMP is readily available**
  - **Patients at high dosages report decreased renal function and greater accumulation of drug [1]**
  - **Decreased renal function causes patients to also present with hypercalcemia and hepatotoxicity**
  - **The maximum dosage at which this drug can be administered without affecting renal function has been found to be 0.15 mg/kg/h, 3 days a week [1,2]**
- **The cellular pathways effected by 8-Cl-cAMP are under investigation**
  - **Evidence has suggested the drug operates through p38 MAPK activation inducing apoptosis via extrinsic pathways [3]**
  - **These effects have already been paired synergistically with existing chemotherapies, including Paclitaxel [4]**
- **Conversion of 8-Cl-Adenosine to 8-Cl-cAMP has been observed [5]**
  - **This ability to be interconverted illustrates that the effects of 8-Cl-cAMP can be supplemented with the less toxic prodrug, 8-Cl-Adenosine**

Patient Selection Criteria & Treatment

- **Diagnosis of lymphocytic leukemia**
- **Rai Stage III or IV & 18 years or older**
- **Zubrod performance status less than or equal to 2**
- **Dosage of the Intravenous Treatment:**
  - **8-Chloro-Adenosine = 45mg/m²/hr**
  - **8-Chloro-cAMP = 0.15 mg/kg/hr**
  - **One hour per treatment, 3 times/week for 4 weeks**

Conclusion

Based on the evidence provided from 8-Cl-cAMP clinical trials, it is clear that this drug is a powerful tool that can be used to treat various types of cancer. This benefit comes at a price, however. The drug's solubility means that plasma concentrations are harder to control. This is normally corrected by increasing the drug's concentration, resulting in toxic side effects. This was seen in the clinical trials which brought about a decrease in research on this drug; many felt that the side effects were too costly for patients. However, adding the prodrug 8-Cl-Adenosine may be able to minimize the side effects while maximizing the therapeutic effects. This is due to the convertibility of 8-Cl-Adenosine to 8-Cl-cAMP. Adding 8-Cl-Adenosine would allow for the lowering of the 8-Cl-cAMP dosage as the body will produce this product as it converts 8-Cl-Adenosine. This also alleviates the need for time delayed delivery systems. This conversion takes time, meaning that the body will produce 8-Cl-cAMP at a constant rate, leveling the plasma concentration over longer periods of time. The combination of the conversion properties and the time it takes for the conversion to complete indicate that a combination of 8-Cl-cAMP and 8-Cl-Adenosine would provide the maximal therapeutic benefits with minimal side effects. These two drugs are thus prime targets for a combined clinical trial.

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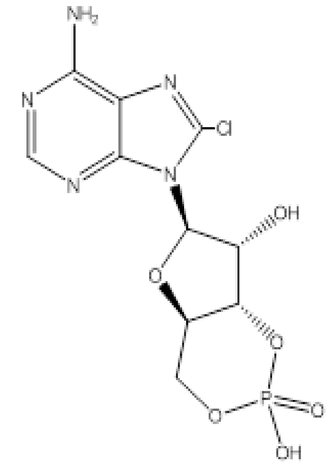

8 - Chloro - cAMP (8 - Cl - cAMP)

Acknowledgments

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