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Insulin Induced Hypoglycemia during Chemotherapy as a Prelude to Treatment in Advanced and Recurrent Head and Neck Cancer: A Prospective Trial

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Abstract

Normal cells and cancer cells can be differentiated clearly during hypoglycemia because of the difference in the number of insulin receptors and the biologic response modification which insulin produces. This helps in targeting the chemotherapy drugs more specifically and effectively inside the cells. This occurs with reduced doses of chemotherapy drugs and minimizes their side effects. With this aim two patients with advanced and recurrent Head and Neck cancer were included in this pilot study and about one tenth the dose of chemotherapy with Carboplatin 75 mg and Gemcitabine 200 mg were given once weekly for six weeks during period of hypoglycemia produced every time by giving intravenous Insulin 0.1ug/kg. A complete response was achieved in one patient and other patient had a partial response and which responded to radiotherapy achieving a complete response. There was no side effect of the drug or hypoglycemia recorded by the patient. The survival was 11 months and 8 months respectively concluding that even one tenth the dose of chemotherapy given during hypoglycemia gives a very good clinical response with no side effects of the drugs.

Keywords: Insulin potentiation; Hypoglycemia; Low dose chemotherapy; Recurrent cancer.

Introduction

Chemotherapy drugs in high doses are required to force themselves across the cell membrane to produce powerful cell killing. This causes serious dose related side effects because chemotherapy agents do not discriminate between cancer cells and normal cells, killing both types of cells.

Dr. Donato Perez Garcia of Mexico in 1926[1] innovated new drug delivery technique called Insulin Potentiation Therapy (IPT). Insulin is a powerful harmone managing the delivery of glucose across the cell membrane. It communicates its messages to cells by joining up with specific insulin receptors scattered on the outer surface of the cell membranes. Every normal cell in human body has hundreds of receptors but cancer cells have 6 to 15 times more of such receptors. It is a well known fact that cancer cells have a voracious appetite for glucose and they virtually steal it away from the body's normal cells thus starving them. The excess of insulin receptors in cancer cells increases the permeability of cell membranes leading to increased intracellular concentration of chemotherapeutic drugs which is not seen in normal cells.[2,3]

Chemotherapy drugs like to attack rapidly dividing cells and in a tumor all cells are in different stages of cell cycle at one time. In a tissue culture experiment insulin along with insulin receptors stimulated growth in many of the cells that were not in the growth phase. This metabolic modification by insulin rendered more of these cells to chemotherapy attack contributing to increased death rate.[4,5]

Because of this important element of differentiation along with biologic response modification which insulin produces, very low doses of chemotherapy drugs get targeted more effectively inside the cancer cells. Cancer cells die; tumor shrinks and no side effects are seen in normal tissues. IPT appears to be wonderful new way of treating cancer using the conventional chemotherapy drugs in very

low doses.

Case report

A prospective study to know the actual effect of low dose of chemotherapy drugs during hypoglycemia was done. Patients with recurrent head and neck cancer who have nothing more to be offered were included in this study. A written informed consent regarding the procedure, including death due to hypo-glycaemia was obtained from the patients and their close relatives.

The aim was to achieve minimum blood sugar level of 50 mg% and to give one tenth dose of conventional chemotherapy drug during period of induced hypoglycemia and then normalize the blood glucose with oral and parentral glucose. Blood sugar levels, cardiac and neurological status was monitored before starting the treatment and also constantly during the period of hypoglycemia which lasted for about half hour. Chemotherapy was given every week for six weeks with close monitoring of disease and side effects of drugs and hypoglycemia.

This prospective pilot study included two patients of advanced and recurrent Squamous cell carcinoma of buccal mucosa. One patient had recurred after he underwent surgery and radiotherapy twice and the other had recurred after surgery and chemotherapy. Both these patients have nothing more to be offered except palliation so they were included in this trial.

Complete pretreatment evaluation was done for hematological, renal, hepatic, cardiac and neurological status which was normal in both patients. During chemotherapy patients were kept in intensive care unit with cardiac monitor and pulse oximeter on for continuous monitoring. Blood sugar was monitored closely during hypoglycemia phase for chemotherapy.

Premedication with Granicetron 3mg and dexona 8mg was given. Then Human Insulin 0.1mg/Kg was given intravenously. Blood sugar was done every 5 min and as soon as it was below 50 mg%, chemotherapy with Carboplatin 75 mg and Gemcitabine 200 mg were given as infusion over 15 min. Then oral fruit juices and dextrose 10% infusion were given and normal blood glucose was achieved. During period of hypoglycemia both patient had hot flashes, tachycardia, dryness of mouth, perspiration from which they recovered as soon as normal glucose level was achieved. There were no cardiac or neurological symptoms or signs recorded. Patients were fully conscious and oriented during the procedure. The same procedure and drugs were given every week for six weeks with close monitoring. During follow up period a close watch on the disease, cardiac and neurological status was kept. ECG was done during each visit to see any changes.

Fig 1: Pre treatment case of recurrent carcinoma buccal mucosa showing large growth

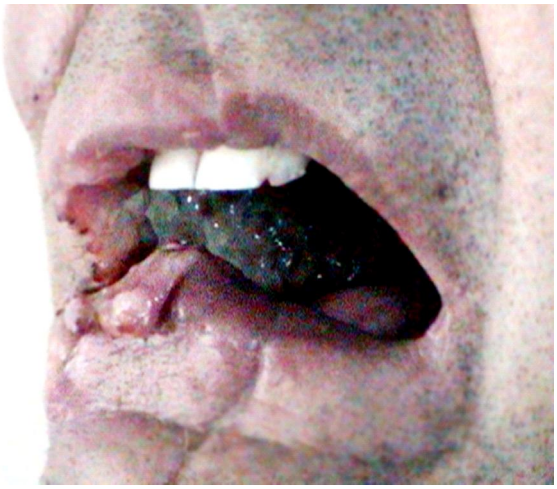
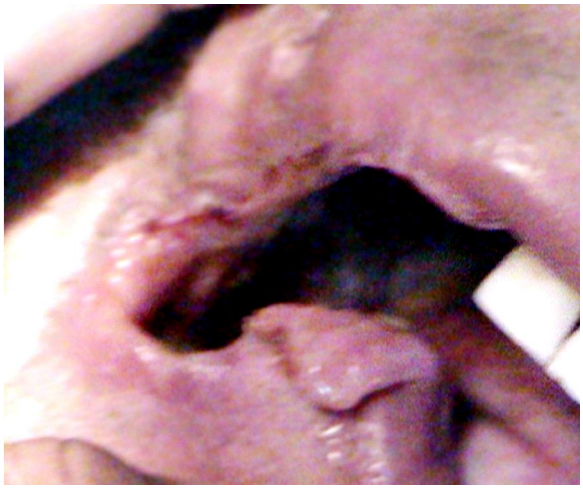


Fig 2: Six months post treatment showing complete regression of tumor with increase in size of oro cutaneous fistula



Results

Both patients had a good response to insulin potentiated chemotherapy. After completing six cycles one patient had a complete clinical response although there was increase in size of orocutaneous fistula and the other had a 75% reduction in size of tumor. Both the patients had tachycardia, perspiration, hot flushes and dryness of mouth which were temporary and reverted back to normal once the blood sugar was normal. None of the patients had any cardiac or neurological signs or symptoms either during the period of hypoglycemia or until their last follow-up. There was no Neutropenia, anemia, alopecia and loss of appetite seen as is routine with high doses of chemotherapy. Thus the tolerance to hypoglycemia was good with a good clinical response. One patient with partial response took radiotherapy and achieved a complete response. Astonishingly both the patients did not develop any nodal or distant metastasis during follow up, although no comments can be made on this aspect on this small study. The survival in these patients was eight months and eleven months respectively. The short term hypoglycemia did not have any cardiac or CNS side effects and is safe.

Discussion

IPT is a questionable cancer therapy that uses insulin as an adjuvant agent to potentiate the effect of chemotherapy. Advocates of IPT believe that cancer cells consume more sugar than healthy cells and therefore cancer cells are more sensitive to insulin and insulin like growth factor.[2,3] Insulin is also believed to increase the permeability of cell membrane increasing the intracellular concentration of anticancer drugs.[1] According to the theory behind the therapy, cancer cells contains ten times more insulin receptors in cell membrane and can be activated by exogenous insulin and one tenth dose of chemotherapy drug can provide the same cytotoxic effect with less severe adverse reaction. In multidrug-resistant metastatic breast cancer, methotrexate with insulin produced a significant antitumoral response that was not seen with either methotrexate or insulin used separately.[6] No clinical trial has been performed to validate this claim. Currently there is no data comparing the efficacy of I P T to conventional chemotherapy.

In our pilot study a definite clinical response with low doses of chemotherapy with insulin is seen meaning that there is an increased susceptibility of the cancer cells for chemotherapy drugs during hypoglycemia. Tolerance of patients to hypoglycemia is good with no side effects either early or delayed. Even there are no delayed cardiac or neurological side effects. So we conclude that good tolerance and a good clinical response in patients who have failed to all modalities of cancer treatment previously are achieved. So this method of drug delivery should be studied further and more randomized trials should be done to conquer the side effects of the drugs without compromising with the results.

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