Role of Low Dose Cisplatin Under Insulin Induced Hypoglycaemia in Advanced Head and Neck Cancers: A Prospective Study

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Abstract

Normal cells and cancer cells can be differentiated clearly during insulin induced hypoglycaemia because of the difference in number of insulin receptors on cell membrane as well as the biologic response which insulin modifies. This helps in targeting the chemotherapy drugs more specifically and effectively inside the cells. Under insulin this occurs in cancer cells with low doses of chemotherapy drugs with lesser side effects. With this aim we did this randomised study in advanced head and neck cancer cases comparing low doses of cisplatin under hypoglycaemia with usual weekly dose of cisplatin along with full dose of radiotherapy. There was 77.7% complete response and 11.1% partial response in low dose and 90% complete respone in full dose chemotherapy with minimal side effects in low dose arm and no neurologic or cardiac toxicity was observed in hypoglycaemia arm. Thus we conclude that the use of low dose chemotherapy is equally effective with minimum side effects when given under hypoglycaemia.

Keywords: Low Dose Chemotherapy; Hypoglycaemia; Insulin; Head & Neck Cancer.

INTRODUCTION

As per Globocon 2020, 1 in 5 people develop cancer during their lifetime, and 1 in 8 men and 1 in 11 women die from the disease. Ageing

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populations globally and socio-economic risk factors remain among the primary factors driving this increase.[1] Head and neck cancer is one of the most commonly occurring cancer worldwide, it accounts for approximately 573775 cases in males and 171219 cases in females. It has a higher incidence in Asia because of the high consumption of smokeless tobacco. Incidence of head and cancer in India is 219722 that is 29.5%, and is third most common cancer in India.[1]

Treatment of early stage (stage I or II) head and neck cancer is surgery or radiation therapy which is usually recommended for approximately 30-40% of patients. Both the treatments have almost equal survival. For advanced staged cancer, combined modality approach involving surgery and or radiation therapy with chemotherapy have shown

improved outcomes. Recurrence and relapse are quite common in advanced stages of head and neck cancer. The National Cancer Comprehensive Network also recommends that such patients be ideal candidates for clinical trials and not the conventional approach. One of the options for such patients is the use of Metronomic Chemotherapy, which is the use of chemotherapeutic agents in a timed manner to achieve local control and prevent progression of the disease. Chemotherapeutic drugs are required for significant action and to force itself through the cell membrane of cancer cells to produce cell killing. Chemotherapeutic drugs being cytotoxic not only affects the cancer cells but also has effect on the normal cells there by causing serious chemotherapy induced toxicities.

Insulin Potentiation Therapy (IPT) is one of the newer and relatively safer approaches to treat cancer. Chemotherapy drugs in high doses are required to force themselves through the cell membrane to produce cell killing. As the drug cannot differentiate between a cancer cell and a normal cell hence equal concentration of drug is pushed in all cells causing serious side effects. Dr Donato p Garcia innovated a novel drug delivery system called Insulin Potentiation Therapy. It is a well known fact that insulin manages delivery of Glucose across the cell membrane. It does this through the insulin receptors present on the cell membrane. It has been found that there are hundreds of these receptors present on the normal cell membrane but cancer cells have 6 to 15 times more receptors on their cell membrane. It is also a fact that cancer cells have a voracious appetite for glucose hence it takes up all letting the normal cell to starve. Increased number of Insulin receptors on cancer cell membrane increases the permeability of chemotherapy drug into the cancer cells leading to increased concentration of the drug into the cancer cell then normal cell.[2,3] This differential effect may help reduce the drug dose to one tenth the normal under hypoglycaemic conditions producing same effect on cancer cell and reducing the drug toxicity as concentration of drug is very less in normal cell. Hence Insulin Potentiation therapy becomes a potential way of treating cancer using conventional chemotherapy drugs in very low (about one tenth) dose producing similar effects with very less toxicity.

We planned this study in advanced head and neck cancer using very low dose of cisplatin concurrently with radiation therapy in order to see the response with low dose of chemotherapy given under hypoglycemic conditions.

MATERIALS AND METHODS

This is a prospective randomized study started after getting ethical approval from the institutional ethics committee and taking in formed Consent from the patient and relatives.

Patients with Stage IV Head and Neck cancers with no prior treatment and without any neurological and cardiovascular morbidities, no history of diabetes, hypertension and epilepsy between age 30-70 years with KPS score of more than 70% were included in the study. A total of 20 patients fulfilling the inclusion and exclusion criteria with advanced staged head and neck cancer were taken into the study and were divided into two groups on alternate basis. The overall survival was measured from the startof therapy till the last follow up and or death of the patient and was assessed till October 2022.

All stage IV patients of Head and Neck cancers were evaluated clinically, radiologically and their Electro cardiogram, Echo cardiogram, audiometry and neurological evaluation was done by the physicians. If they fitted in the inclusion criterion then they were randomized into two arms. All the patients in both the groups received radiotherapy with Intensity modulated technique to a dose of 66Gy in 33 fractions in 45 days on Varian Clinac linear accelerator. For concurrent chemotherapy the patients in arm 1 received chemotherapy with Cisplatin with a dose of 10mg weekly under hypoglycaemic condition once weekly for 5 to 6 times while patients in arm 2 received Chemotherapy with Cisplatin with dose of 30mg/m2 weekly with hydration under normal conditions once weekly.

For chemotherapy under hypoglycaemia patients were shifted to intensive cardiac care unit and a proper cardiac and neurological evaluation was done by a physician and then was given regular Insulin at a dose of 1mg/kg intravenously and blood glucose was seen every 10 minutes. As soon as the blood glucose reached to 50mg/dl then injection Granisetron 3mg was given in 100ml normal saline and inj Cisplatin 10mg was also given in 100ml normal saline over 15 minutes.The patient was kept in a state of hypoglycemia for 10 minutes, and the blood sugar was reverted back to normal by administration of oral fruit juices and intravenous dextrose 10%.

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infusion till the normal blood sugar level was achieved and 500 ml of saline was continued over 2 hours.

Patients in arm 2 received Chemotherapy with Cisplatin 30mg/m2 in wards, with Pre medications, hydration and post medications consisting of Granisatron 3mg, Aciloc 50mg, Dexa 8mg in 500 NS. KCL, mgso4, Vitamin, Mannitol was also given as supplements.

All patients were assessed weekly and after giving 6th cycle chemotherapy and completion of radiation for toxicity and local control. After one month of completion of treatment patient were assessed for response evaluation which was done according to *Recist Criteria* (Response evaluation criteria in solid Tumors) version 1.1.

OBSERVATION AND RESULTS

A total of 20 patients were enrolled in this study. 10 Patients in ARM 1with Low dose cisplatin under hypoglycemia with radiation and ARM 2 with normal dose cisplatin with radiation. The median age was 45 years (range – 35 to 60 years). Buccal mucosa (BM) was the most common site of tumor. All of the tumor's histology was squamous cell carcinoma.

18 out of 20 patients had stage IVA disease and 2 patient had stage IVB disease. Most of the patients had a performance status of 80% according to the Karnofsky Performance Status (KPS) scale. All the patients were screened for neurological and cardiac toxicities, that included history of seizures, cerebrovascular accident, arrhythmias, ischemic heart disease, hypertension, or diabetes; and none of them had any above mentioned toxicity before starting the chemotherapy and it had been certified by and fitness was obtained from the department of neurology, cardiology and internal medicine.

1 patient did not complete 6 cycles of chemotherapy in arm 1 and was lost to follow up rest all the patients in the both arm completed the planned chemotherapy and radiation therapy.

7 of the patients had a complete response, 1 patient had partial response and 1 had (first stable response) then progressive disease as patient later on developed subcutaneous metastasis and 1 patient defaulted during the chemotherapy in arm 1 (Fig. 1,2,3) whereas in arm 2, 9 patient had

Fig. 1: Pretreatment carcinoma tongue showing extensive growth involving base of tongue also with Fixed Tongue

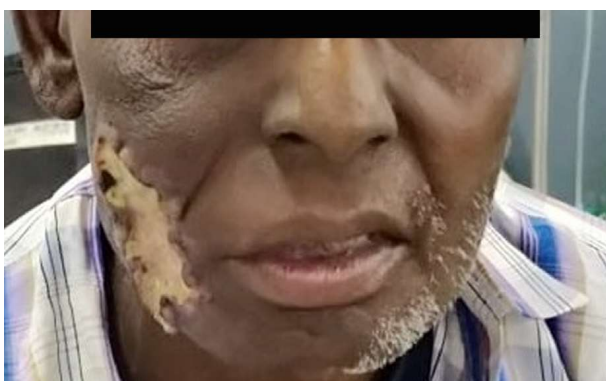**Fig. 2:** Post treatment showing complete regression of growth

Fig. 3: Post treatment carcinoma buccal Mucosa showing complete response.

complete response and 1 had partial response. All the patients had symptomatic relief from pain.

Evaluation after chemotherapy showed that there was complete response in 77.7% of the patient and partial response was 11.1% (Table 1). The overall response was 88.8% in arm 1 and the over all response in arm 2 was 90%. The two-tailed P value of Arm 1 equals 0.01 and for Arm 2 equals

Table 1: Response rates in both arms

Response	Number of patients ARM 1	Percentage (%) ARM 1	Number of patients ARM 2	Percentage (%) ARM 2
Complete Response	7	77.77	9	90
Partial Response	1	11.11	1	10
Stable Disease	0	0	0	0
Progressive Disease	1	11.11	0	0

0.008. By conventional criteria, this difference is not statistically significant, but there is a reduction in size noted.

Toxicities were measured as per CTCAE version 5. Neurological toxicities evaluated during period of hypoglycaemia and during follow up were Seizures, Somnolence, Headache, Coma And Tremors. None of the patients developed seizures during the period of hypoglycemia. Around 6 patients had somnolence, out of which 4 hade grade 1 Somnolence and 2 had grade 2 somnolence, which was recovered once the blood sugar was back to normal. 4 patients developed headache, out of which 3 had grade 2 headache while the 1 patient had grade 3 headache, but headache was due to the extensive disease and not due to hypoglycemia. All the patients had tremors and were soon recovered after the blood sugars were back to normal. None of the patients developed coma. Cardiac toxicities evaluated were Sinus tachycardia, Palpitations, ECG changes (arrhythmias and cardiac ischemics). All the patients developed tachycardia during the period of hypoglycemia which was of grade 1 intensity. 6 patients developed palpitations. All of these toxicities were reverted back to normal once normal blood sugar was achieved. None of the patients developed any fatal arrhythmias or any cardiac ischemia which were continuously monitored by cardiac monitor. Follow up ECG also did not showed any changes.

4 patients had hot flashes, 8 patients had hyperhidrosis, out of which 2 had grade 2 hyperhidrosis and 6 hade grade 3 hyperhidrosis but it was recovered as soon as the blood sugar level was normal and hydration was given to the patient. 2 patient had developed myelosuppression (leucopenia) during the chemotherapy their total leucocyte count (TLC) was less than 3000, for which they had been given subcutaneous filgrastim, later on recovered from the disorder and the chemo was continued.[4] patients developed hypokalemia due to intravenous administration of insulin to achieve hypoglycemia, though they were no significant

electrocardiogram (ECG) changes, it was managed by giving patient oral potassium supplements and high potassium-rich diet. 1 patient developed hyperkalemia.

2 patient had developed vomiting out of which 1 had grade 1 vomiting and another had grade 2 vomiting. No patient had developed nephrotoxicity, or ototoxicity, or a raise in serum AST levels during the chemotherapy sessions. 1 patient had developed grade 1 alopecia.

After completion of the prescribed 6 cycles of chemotherapy in both the arms, there were no neurological or cardiac toxicities due to insulin induced hypoglycemia in all patients.

Headache was present in 3 patients, out of which 1 had grade 2 headache while the other patients had grade 1 headache, but the headache was due to the extensive disease and not due to hypoglycemia. No patient developed vomiting, and 1 patient developed grade 1 alopecia, 1 patient developed myelosuppression in arm 1. Whereas 4 patients in Arm 2 had myelosuppression which was recovered after giving Colony stimulating factorsand two had grade I alopecia. No patient had toxicities that they had during the period of hypoglycemia during their follow up. None of the patient had developed nephrotoxicity, or ototoxicity had a raise in serum AST levels after the completion of 6 cycles of chemotherapy in either arm.

Over all survival was measured from the start of therapy till the last follow up and or death of the patient. The median survival rate was 11 months in ARM 1 where as in ARM 2 it was was 11.5 months. The death of the patient was not due to neurological or cardiac cause.

DISCUSSION

IPT has been 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 glucose than a

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normal healthy cell and hence are more sensitive to insulin and insulin like growth factors.[2,3] Insulin also increases the permeability of the cell membrane thus increasing the intracellular concentration of anticancer drugs.[4] According to the basic theory behind this therapy it is told that cancer cells contain 10 times more insulin receptors in the cell membrane and insulin given during therapy activates these receptors and hence only one tenth dose of chemotherapy drug can provide the same cytotoxic effect with less adverse reactions.

Otto Warburg in 1924 demonstrated that cancer cells were dependent mainly on glycolysis for the manufacture of energy even in the presence of oxygen. Accordingly, cancer cells require approximately 20 times more glucose amounts in comparison to normal cells. This Warburg effect is also the concept behind PET CT imaging, where FDG is taken up by malignant cells in contrast to normal cells.[5] In light of the concept of Warburg effect we used very low doses of chemotherapeutic agents under hypoglycemia in advanced head and neck cancer cases. Gary *et al.* demonstrated that insulin induces a Metabolic modification effect to cause an increment in the S-phase fraction in cancer cells[6,7] hence allow the chemotherapy to work and slow down the multiplication of the cancer cells.Cisplatin has shown very good response for head and neck cancers[8] and hence we have used cisplatin as one of the chemotherapeutic agent inour regimen.

Lasalvia and Prisco in their randomized control trial in metastatic breast cancer showed that the median increase in tumor size was significantly lower with insulin used along with methotrexate than when they were used separately suggesting the enhanced effect of methotrexate under hypoglycaemia.[9]

S.G. Ayreetal in their study had found that low doses of chemotherapeutic drugs under insulin induced hypoglycemia were equally effectivedue to increased intra cellular dose and effect of chemother apeuticagents. With lower systemic chemotherapeutic drug doses but having higher intracellular drug successfully harm the cancer cells.[10] Bhandari et al in their case report of two patients treated with low dose cisplatin under insulin induced hypoglycemia one had a complete response while other had a partial response and both patients developed hot flashes, tachycardia, and palpitations without developing any nodal or distant metastasis.[11] Oliver alabaster *et al.* showed that breast cancer patients treated with insulin and methotrexate 75% showed partial response along with lower incidence of distant metastasis as compared to patients treated with methotrexate alone where 12% patients showing partial response and 88% had progressive disease, stating that insulin enhances the cytotoxicity of methotrexate.[12]

In a study Clinical benefit was seen in a few patients from reintroduction of trastuzumab, low dose chemotherapy along with insulin. The explanation of this prolonged response is only speculative and requires further clinical confirmation. In another study where low dose chemotherapy and harmone therapy was used with Insulin induced hypoglycaemia in Castration-Resistant Prostate Cancer and 16 completed 6 cycles. 50% showed partial response, 25% had stable disease and progression was seen in other 25%. Usually the improvement occured after the 2nd cycle. After the 10th IPT cycle in 9 patients complete response was seen in 33%, partial response in 11%, stable disease in 22% and progression in 33%. All these study show that low dose chemotherapy works equally under hypoglycaemia as does full dose chemotherapy.[13]

In our study also where we compared full dose of chemotherapy with low dose of chemotherapy along with radiation in advanced head and neck cancer we found complete response in 77.7% of cases with low doses comparable to full dose chemotherapy but with lesser side effects and no neurological or cardiac toxicity was seen due to hypoglycaemia.

CONCLUSION

We included 20 patients divided into two groups and saw that both the groups have almost similar response with reduced toxicity in hypoglycaemic arm. The tolerance of treatment was also good and no toxicity was seen in patients due to hypoglycaemia. Hence we conclude that the short period of hypoglycaemia is very well tolerated without any side effects and the goal of achieving equivalent response with lesser toxicity is achieved. So this modality of drug delivery of low dose chemotherapy (one tenth of the full doses) during hypoglycaemia should be studied in more number

of patients and in various types of cancer such that we achieve similar results with reduced toxicity of the drugs. A draw back to this study is a small sample size hence more studies with increased sample size in different types of cancers should be done to establish this novel drug delivery system.

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