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RESEARCH ARTICLE

METFORMIN'S ROLE IN RESPONSE TO INDUCTION CHEMOTHERAPY FOR MULTIMODAL TREATED HEAD AND NECK CANCERS IN DIABETIC PATIENTS

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ABSTRACT

Head and neck squamous cell carcinoma (HNSCC) is the sixth most common malignancy and recent sequencing of the HNSCC genomic demonstrate the potential of targeting the m-TOR pathway in the treatment of these malignancies. Metformin is one of the most widely prescribed oral anti-diabetic drug but some preclinical evidence suggesting that metformin has anti-cancer properties leading to the inhibition of m-TOR pathway.Metformin plays also a role in modulation of the immune system by potentiating the action of T lymphocyte on the tumor cell and reduces the Warburg effect characteristic of the tumor cell where tumor cells generate ATP from glycolysis in conditions of poor nutrition and hypoxia. The association of Metformin with platinum-based chemotherapy and radiotherapy has shown in some studies potentially synergistic and radio-sensitization.

Some trials demonstrate the benefit of sequential chemotherapy, (induction chemotherapy followed by radiotherapy or concurrent chemo-radiotherapy). The purpose of the study is to evaluate comparatively the imaging response (RECIST CRITERIA) to induction chemotherapy in patients diagnosed with diabetes and head and neck cancers treated with Metformin or not with the induction chemotherapy response of patients without metabolic comorbidities. The results can comparatively evaluate the platinum sensitivity for diabetic patients and the influence of Metformin in the modulation of this sensitivity.The study also aims to compare the benefit of induction chemotherapy to patients who associate diabetes mellitus with advanced local head and neck cancers proposed for multidisciplinary treatment.

INTRODUCTION

Metformin is an oral anti-hyperglycemic drug which acts by inhibition of the mitochondrial complex I and oxidative phosphorylation. Several studies have shown correlations between improved outcomes in head and neck squamous cell carcinoma and the administration of Metformin. The mechanism of action involves disruption of tumor metabolism and alteration by immune mechanisms of the tumor microenvironment. The antineoplastic activity of metformin varies depending on the metabolic status of the patients and the molecular particularities of the tumors. Adenosine monophosphate-activated protein kinase (AMPK) has been shown to be primarily responsible for the antineoplastic effects of metformin [1]. The American Diabetes Association and the American Cancer Society formulated some consensus on the link between risk factors, common biological and prognostic features in diabetes and cancer[2].

MATERIALS AND METHODS

The study included 30 patients diagnosed with non-metastatic squamous cell carcinoma of the head and neck.The analyzed cases included squamous cell carcinomas of oropharynx (12 cases),hypopharynx (2 cases), larynx (9 cases) and floor of mouth(7 cases). Patients who were staged using CT imaging pretreatment followed induction chemotherapy of 2-4 cycles

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and who were evaluated for CT imaging were included. Induction chemotherapy included platinum-based monotherapy, platinum-taxanes doublet (TP) or platinum-5-fluorouracil (PF) or triple association platinum-taxane-5-fluorouracil (TPF). 6 patients received Carboplatin or Cisplatin monotherapy, 16 patients received TP or PF platinum doublet 8 patients received triple association TPF protocol. Subsequently, all patients received intensity modulated radiotherapy (IMRT) or volumetric arc therapy (VMAT) with curative intent. Radiotherapy was delivered using the sequential boost technique up to a total dose of 70Gy in 35 fractions on primary tumor volume, 66Gy in 33 fractions on the high-risk cervical lymph nodes target volume and 50Gy in 25 fractions for the target the low-risk supraclavicular node volume.Patients receiving concomitant chemo-radiotherapy and patients who did not benefit from the response to chemotherapy induction were not included in the study. 3 patients in the study group were diagnosed with diabetes and received treatment with Metformin at the time of diagnosis of diagnosed diabetes with diabetes. Patients were aged between 46 and 67 years, diabetic patients aged 58.6, respectively 67 years. Diabetic patents associated comorbidities like hypertension and dyslipidemia corresponding to the profile of the metabolic syndrome. Hemoleucogram and biochemistry were analyzed weekly and established. Treatment related toxicities were evaluated using the CTCAE version 4.02.Acute toxicity was evaluated during treatment and supportive treatment was given. for all patients who developed oral mucositis, body weight and fluid balance were monitored. Mouth washes with local analgesics, coating agents or anti-inflammatory corticosteroids were administered in all cases with caution on blood glucose levels and the risk of hypertension.

RESULTS

No patient had fully responded to induction chemotherapy; 12 patients had partial response (PR), 8 patients had stable (SD) disease and 5 patients had disease progression (PD). All diabetic patients.For all diabetic patients, PF or SD was obtained after induction chemotherapy.

DISSCUTIONS

A study by Baur *et al* highlighted an increased risk of mortality among diabetic patients and for those treated with insulin the relative risk was 2-4 higher compared to the non-diabetic cancer patients. The authors conclude that both diabetes and associated treatments increase the risk of mortality among patients diagnosed with cancers except for patients treated with Metformin[3].

Alcusky *et al*. evaluated the effect of Metformin exposure after the diagnosis of head and neck cancers on the risk of all-cause mortality in a population-based Italian cohort. The authors analyzed 7,872 patients, 708 (8.99%) exposed at some point after the diagnosis of cancer to metformin. 3,626 (46.1%) died during a 2.98 years median follow-up.The authors failed to identify a significant association between exposure to metformin and reduced risk of all-cause mortality in case of head and neck cameras without being able to prove validated theories in preclinical studies[4].

Although systematic review and meta-analysis demonstrate the improvement in the overall survival of the majority of patients diagnosed with cancer and treated with metformin, especially colorectal cancer, bronchopulmonary hepatocellular carcinoma, on a cohort of Ontario diagnosed with squamous cancer of the larynx, hypopharynx, and nasopharynx no survival benefit was observed [5],[6].

In a study conducted in patients diagnosed with oropharynx cancer treated by chemotherapy with modern techniques, Spratt *et al*. assesses the effect of metformin exposure of diabetic patients on local failure-free survival (LFFS), regional failure-free survival (RFFS), distant metastasis-free survival (DMFS), and overall survival (OS). The stds have demonstrated improved DMFS for nondiabetic patients and improved DMFS for metformin users. LFFS and RFFS were significantly influenced by diabetes status and metformin use [7].

For patients receiving radiotherapy, there are both in vitro and in vivo studies that show the benefit of metformin that can improve the efficacy of radiotherapy for cancer patients who have diabetes, assessing short-term response and long-term survival with 2-year and 5-yearoverall survival endpoints. Patients who received metformin had survival benefits and short-term response compared to patients who were not treated with metformin[8].

Patients receiving metformin treatment also have a risk of losing weight caused by reduced food intake, loss of appetite and gastrointestinal side effects. Weight loss is associated by many authors with an increased risk of toxicity. In patients with head and neck cancers, weight loss is also enhanced by swallowing impairments caused by the tumor itself or by the side effects resulting from multimodality treatment. It is demonstrated that weight loss during treatment is associated with poor prognosis and increased toxicity. Chang *et al*. demonstrates that multimodal treated patients for head and neck cancers require careful multidisciplinary management and support in order to complete treatment without severe associated toxicity, but may also benefit from metformin from a survival point of view[9].

Mutations in tumor protein 53 (TP53) tumor suppressor genes are common in head and neck cancers and metabolic changes from mitochondrial respiration to glycolysis. There is a possibility that glycolysis inhibitors may have a radiosensitizing effect in this subtype of patients. TP53 mutant tumors are radioresistance compared to HNSCC cells that have wild type TP53. Inhibition of respiration using metformin increased glycolysis in wild type TP53 tumors with a possible radiosensitivity effect[10].

Another hypothesis is based on the concept that metformin acts distinctly on stem cells from head and neck cancers and on tumor cells. Cancer stem cells are involved in resistance to conventional chemotherapy. Kuo *et al* demonstrates the effect of metformin on malignant stem cells exposed to Cisplatin chemotherapy, but metformin has reduced the proliferation of non-stem cancer cells. The authors conclude that metformin targets complex III and has the effect of reducing reactive oxygen species, leading to differential effects on stem and non-stem malignant cells[11].

Associating metformin with chemotherapy can benefit but in order to customize the treatment, it is necessary to understand the molecular mechanisms that can lead to potentiation or decrease effects to the cytotoxic effect of chemotherapeutic agents. Induction of apoptotic mitochondria and nucleus could be the explanation for the synergistic effect of metformin combination with cisplatin and down-regulation of lipoprotein or cholesterol synthesis may be molecular base theory forthe effect of metformin in association with taxanes[12].

Other authors associate metformin in the treatment of cancer with tumor-targeting microenvironment and suppression of inflammatory signals. The potential for metformin to target Axl and Tyro3 receptor tyrosine kinase ihniband cell proliferation and to action on Cisplatin resistance has been demonstrated in ovarian cancer[13].

Preclinical research studies proved a synergy between immune-oncology drugs and metformin, demonstrating increase in response rate in the murine B16 melanoma model and MC38 colon adenocarcinoma model using an association between inhibitors of PD-1 combination with metformin, effect not observed for patients receiving metformin alone. The authors also demonstrated that metformin differentially impacts subtypes of head neck cancers, a higher rate of apoptosis being identified in HPV-compared to HPV + carcinomas[14].

To elucidate the mechanisms of clinical benefit to some cancers of the head and neck bymeformin adminstration, we must take into account the new Warburg effect theory. Initial theory ruled that cancer cells metabolize glucose through aerobic glycolysis and normal cells become cancerous since glucose metabolism is altered from oxidative phosphorylation to aerobic glycolysis. Current theory states that Warburg effect corresponds to the initial stage of carcinogenesis and is mediated by one of the known carcinogens (excess carbohydrate in food).

Metformin has been shown to be beneficial in preclinical and clinical studies by inhibiting the m-TOR pathway in prostate, pancreatic and breast cancers, with the implication that m-TOR pathway inhibition is not the only mechanism by which metformin has antineoplastic action[15],[16],[17],[18].

In a preclinical study, Verma *et al*. treated severe combined immunodeficient (SCID) mice bearing orthotopic head and neck squamos cell xenografts treated with metformin for 5 days evaluated tumor oxygen saturation and hemoglobin concentration and observed increases in these values in the treated group compared to the control group and also a significant decrease in Ki-67 staining and MR-based tumor volume in the group of mice exposed to metformin.The authors conclude that the administration of metformin induces changes in tumor microenvironment[19].

In a cohort of patients taking metformin compared to patients not taking metformin incidence of head and neck cancer was 0.64 times lower and a lower incidence for patients> 40 years old taking metformin.However, evidence of clinical efficacy in therapeutic associations in head and neck cancers is limited to several studies. The most extensive systematic review and meta-analysis performed by Decensi *et al*. (2010) of metformin and cancerrisk in diabetic patients, did not analyze head and neck cancer patients [20],[21].

CONCLUSIONS

The presence of diabetes did not negatively influence the response to induction chemotherapy, but it is likely to increase the rate of complications and prolong the time until the beginning of radiation therapy. Other prognostic and predictive factors for toxicities (smoker status, presence of HPV infection, Charlson index of comorbidities, presence of diabetes complications) should be analyzed in relation to the response of diabetic patients diagnosed with head and neck cancers to induction chemotherapy on a larger lot of patients.

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