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CLINICAL STUDY

Implications of diabetes in head and neck cancer – A single center real-world data

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ABSTRACT
Diabetes mellitus (DM) and altered glucose metabolism have been associated with carcinogenesis, but also with prognosis and tolerance to treatment in different types of cancer. Head and neck cancers (HNC), the sixth most common malignancy worldwide, require a multimodal approach, especially in advanced stages and cancer specific treatment is often associated with therapeutic failure and severe toxicities even if it is delivered according to current standards. The aim of the study was to evaluate the clinical, biological and outcomes implications of DM in patients with HNC. The cases diagnosed with HNC associated with DM between January 2008 and December 2016 were selected from the database of the oncology clinic and the oncology outpatient clinic of the Craiova County Hospital. Under the limits of a relatively reduced patient lot of 23 cases, certain particular aspects of these cases are highlighted possibly due to the association of DM with HNC. This category of patients should not be treated differently even if a precaution is necessary due to the increased risk of complications related to treatment. The use of Metformin could bring outcome benefit and the treatment of DM with insulin could be associated with a worst prognostic. The use of poly-chemotherapy regimens (platinum double or triple combination including platinum salts) demonstrates the feasibility of using chemotherapy for these subtypes of patients. A tendency to de-escalate the treatment by omitting radiotherapy for this category of patients should also be noted. Neutrophil to lymphocyte ratio (NLR), a less specific biomarker could be less useful than the Glasgow Prognostic Score (GPS) which can be considered an accessible biomarker. A large percent of sinonasal cancers compared to the data reported in the literature could be also related to DM. Both this possible association and the benefit of Metformin and 5-Flurouracil must be reevaluated in studies in larger groups of patients *(Ref. 25)*. Text in PDF *www.elis.sk*
KEY WORDS: diabetes, head and neck cancers, metformin, toxicity, outcomes, chemotherapy.

Introduction

Diabetes mellitus (DM) is a chronic disease with increasing incidence among adults. In 2014 an incidence of 8.5 % was reported, 90–95 % being cases with type 2 diabetes. Diabetes is not only associated with a large number of complications including cardiovascular diseases, nephropathy, neuropathy, retinopathy, but it is also mentioned as an independent risk factor of carcinogenesis. Also, diabetes is considered a factor associated with compromising outcomes for cancer patients and an aggravating factor of toxicities related to treatment. Hyperglycemia, hyperinsulinemia and fat-induced chronic inflammation are considered the 3 mechanisms by which DM increases the risk of cancer. Also worth mentioning is the effect of treatment for DM on the evolution of cancer, with both benefits and detrimental effects being reported, depending on the class of pharmacological agents involved. Metformin, an anti-diabetic drug from the biguanide class, has been associated with improved treatment outcomes and prolonged overall survival in various types of cancer. Head and neck cancers (HNC) have been associated with DM, there are numerous common risk factors in relation to lifestyle and advanced age, but the mechanisms linking these two diseases have not yet been fully elucidated (1–4).

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Purpose of the study

Evaluation of the clinical, biological and outcome implications of patients with HNC associated with DM and the evaluation of a possible benefit of Metformin treatment in the evolution of cancer.

Materials and methods

The cases diagnosed with HNC associated with DM between January 2008 and December 2016 were selected from the database of the oncology clinic and the oncology outpatient clinic of the Craiova County Hospital. The nadir biological values of glycated hemoglobin (HbA1c), of C-reactive protein (CRP), serum albumin, but also data on the location of the anatomical segment of HNC, histological type, treatment (chemotherapy and radiotherapy regime), but overall survival (OS) was also evaluated.

Results

23 cases who met the inclusion criteria were identified. The distribution by anatomical subtypes of HNC was nasopharynx – 2 cases (8.7 %), oropharynx – 4 cases (17.4 %), oral cavity – 4 cases (17.4 %), hypopharynx – 2 cases (8.7 %), larynx – 6 cases (26 %), salivary gland – 1 case (4.35 %), sinonasal – 3 cases (13 %). Most of the cases were locally advanced stages of the disease: 13 cases (56.5 %) Stage IVA, 2 cases Stage IVB (8.7 %) (1 case with lung metastases and one case with non loco-regional nodal metastases), 3 cases Stage III (13 %), 1 case Stage IIB (4.35 %) and 4 un-staged cases (117.4 %). All cases were DM type 2, and the specific treatment was in most cases oral antihyperglycemic agents: 10 cases (43.5 %) treated with unspecified pharmacological agents, 7 cases (30.5 %) were treated with Metformin. For 8 cases (34.8 %) the treatment was insulin, and 1 case (4.35 %) was treated both with insulin and oral antihyperglycemic agents. For 15 cases (65.2 %), OS data could be recorded, median OS being 9 months (8.5 to 14.5 months). In the group of patients treated with Metformin, the median OS was 12.3 months (3 to 36 months). Patients who received insulin treatment for DM had a median OS of 7 months (4 to 12 months). The median Hb1Ac value was 8.5 %, 3 cases having Hb1Ac values below 6.5 %. 4 of the 23 cases (17.4 %) had GPS value = 0, and 19 cases (82.6 %) were associated with GPS value 1. 10 cases (43.5 %) had surgical treatment within the multidisciplinary approach and 9 cases (39.1 %) also benefited from external radiotherapy. Polychemotherapy was administered in all cases in platinum double or triple association, the number of sequences varying from 1 to 14. Platinum salts (Cisplatin and Carboplatin) were administered in all cases. 5-Fluorouracil, Docetaxel, Bleomycin and Capecitabine are also included in poly-chemotherapy regimens.

Discussion

Kuo and collaborators analyze the data obtained from 556 HNC stage IVA and IVB patients, including alcohol and betel quid consumers, without significant differences between the group of patients who associate DM or are only diagnosed with HNC. From the point of view of the toxicities associated with the adjuvant treatment by chemo-radiotherapy, the authors identified increased rates of grade ≥ 3 hematological toxicities (67 % vs 39.3 %), but DM was associated with lower rates of severe mucositis. Being a study in a population from Taiwan where betel quid is endemic, this risk factor for both cancer and DM is mentioned. Weight loss during treatment is also identified as a factor with a detrimental effect. The authors also mention the lower rate of recurrence free survival (RFS) in the DM group at 1 year (13.1 % lower than in the non-DM group), although both OS and RFS are approximately equal in the data analysis at 2 years. The increased risk of infections as well as the higher hematological toxicity in the case of HNC is mentioned in the DM group, being a possible explanation for the reduction of Cisplatin doses and for the lower rates of mucositis reported in the study in the DM group. Infections during chemo-radiotherapy treatment are identified as an independent risk factor for mortality in patients who associate DM and HNC (5).

Foreman et al identifies a percentage of 12.8 % of patients who associate HNC and diabetes, and the authors do not report major OS differences analyzing data from a lot that includes a number of 2498 cases. As a recommendation, the need to treat these patients according to the standards and not to exclude them from the management is mentioned multidisciplinary of the HNC is also specified (6). Metformin, a biguanide drug that has the effect of increasing cellular sensitivity to insulin, has as its mechanism of action the inhibition of gluconeogenesis. It is known that cancer cells have the capacity for glucose consumption and lactate production even in the absence of oxygen, a phenomenon called the Warburg effect. Inhibition of the Warburg effect with the potential to limit tumor progression is reported when 5Fluorouracil-based chemotherapy is associated in oral squamous carcinoma. Inhibition of the hypoxia-inducible factor-1 (HIF-1) and mammalian target of rapamycin (mTOR) pathways and the activation of 5' adenosine monophosphate-activated protein kinase (AMPK) can limit the Warburg effect. Clinical and preclinical data report the benefit of adding Metformin to chemotherapy in colon and esophageal cancer, but for human oral squamous cell carcinoma the in vivo and in vitro study proposed by Harada and colleagues demonstrate the benefit of combining Metformin with 5-fluorouracil both compared to Metformin alone and compared to 5-fluorouracil as the only therapy (7).

Metformin use was reported to have a moderate reduction in the risk of laryngeal cancer in a cohort study conducted by Becker et al in the United Kingdom. Analyzing data over a period of 18 years, the authors concluded that the protective effect of Metformin is associated only with long-term administration. Metformin's potential antineoplastic effect has been highlighted in in vitro and clinical studies, but data on HNC are still limited. The study proposed by Lee et al evaluated the role of Metformin in patients with HNC and DM. 329 cases associating DM and squamous cell carcinoma of the head and neck (HNSCC) treated in the Princess Margaret Cancer Center were included, 195 being treated for DM with Metformin and 134 being treated with other pharmacological agents. The results did not highlight differences regarding OS, recurrence free survival and disease-specific survival at 5 years. Also, no difference was observed between the outcomes of patients treated with Metformin and patients treated for DM with other pharmacological agents. Stokes and collaborators obtained different results analyzing 1646 HNC patients, of which 378 were with DM. The study highlights diabetes as a factor associated with an unfavorable prognosis, OS at 2 years being 65.6 % and 57.7 % for non-DM HNC and DM cases, respectively. If the diabetic patients received treatment with Metformin OS at 2 years was 73.4 %. Based on these data, the authors hypothesize that Metformin should be part of the therapeutic protocol of HNC multidisciplinary approach, being associated with benefit in cancer specific survival. A retrospective cohort study using the Italian Emilia-Romagna Regional administrative healthcare database highlighted modest protective results against all-cause mortality for patients with HNC who also received Metformin treatment for DM. The benefit is identified in the first 2 years of diagnosis, especially in patients ≤ 60 years of age (8, 9).

The correlation between Metformin treatment and the prognosis of patients with HNC was assessed in a meta-analysis that evaluated studies included in the Cochrane Library, Embase, LILACS, MEDLINE and PubMed databases. OS indicators, disease-free survival (DFS) and disease-specific survival (DSS), as well as the involvement of comorbidities, age, smoking and treatment with metformin were analyzed as potential prognostic factors. High Newcastle-Ottawa Scale (NOS) scores were a predictor of metformin benefit. Also age below 65 is associated with a greater benefit of Metformin. It should be mentioned that the general results were positive only for OS, in the case of DFS and DSS there is benefit only for the studies that were not adjusted for comorbidities. The positive results for Metformin were not confirmed by cohort studies including sulfonylureas and exogenous insulin, both treatments, but especially insulin being associated with an increase in cancer specific mortality (10–12).

Preclinical and epidemiological investigations suggest that the metabolic imbalance caused by diabetes could favor carcinogenesis, being correlated with an increased incidence and an unfavorable evolution of HNSCC cases. Upregulation of Akt/AMPK-mTOR pathway, a pathway sensitive to nutrients, is a recognized factor of resistance to Cisplatin. The rapid progression of tongue cancer and the risk of lymph node metastases have also been correlated with DM (13).

Increased neutrophil lymphocyte ratio (NLR) is considered a complex marker of inflammation but also of innate immune status, the increased values being considered prognostic both in cardiovascular diseases as well as in diabetes and cancer. In the case of DM, atherosclerosis related vascular diseases, but also the microvascular complications of DM (early stage nephropathy, retinopathy, diabetic foot ulcer) are associated with this biomarker of subclinical inflammation. Elevated HbA1c and poor glycemic control were correlated with increased NLR values. Mertoglu and colleagues propose, apart from NLR, another biomarker, platelet to lymphocyte ratio for identifying the pre-diabetic state, but also the advanced stages of DM type II (14–16).

A meta-analysis including 24 articles and 6479 cases demonstrates an obvious correlation between increased NLR values and poor prognosis of HNC. The study proposed by Haddad and collaborators mentions a cut-off value of NLR of 5 as a predictor of mortality in HNC cases. Thus, with a median follow-up of 34 months, in a group of 46 patients with HNSCC treated with definitive chemo-radiotherapy, 2 years OS was 89 % vs 61 % for NLR < 5 and NLR ≥ 5. A benefit of 84 % vs 64 % and 81 % vs 70 % was obtained for metastasis free survival and locoregional relapse free survival if NLR was < 5 and NLR ≥ 5 respectively (17, 18).

The Glasgow prognostic score (GPS) is an index of inflammation that was evaluated in order to anticipate the evolution of malignant tumors, but especially of colorectal, gastric and lung cancer. This score is based on the biological values of albumin and C-reactive protein and hypoalbuminemia examined before surgical treatment. Associating an increased value of CRP and hypoalbuminemia, GPS is an indicator of chronic inflammation of the host. GPS = 1 is associated with a worse prognosis than in cases with GPS = 0. Also, the OS for patients with GPS = 2 was reported to be lower than the cases associated with GPS = 1. The identification of new biomarkers is a subject of interest both for prognostic and predictive purposes of response to multimodal treatment. The concept of precision medicine for HNC has included radiomics and artificial intelligence in strategies to identify candidates for an escalation or de-escalation of treatment, complex models including clinical, biological and radiomics data being considered with more accurate predictive potential (19–22).

The modified Glasgow prognostic score (mGPS) also includes C-reactive protein and serum albumin levels. Terazawa el al propose an immune-mGPS (imGPS) that includes the value of lymphocytes. For this purpose, the authors proposed a study that included 461 patients with HNSCC, evaluating ImGPS, as derived from a conventional mGPS. ImGPS also included a criterion for a low number of lymphocytes ($< 1250/\mu L$). The study demonstrated that imGPS offers better accuracy than mGPS in predicting the evolution of patients with HNSCC. mGPS is considered a precise predictor of OS for patients with HNC and after analyzing the data of the study carried out at the University of Tsukuba Hospital including 210 cases of HNC, values of 1 and 2 of the score are associated with worst outcomes (23).

Sinonasal cancer represents less than 0.2 % of all cancers and approximately 3.6 % of HNC. It should be noted that, even if it is a small group of patients, the proportion of sinonasal cancers including maxillary and sphenoid sinus cancers in this study is much higher, an association with DM being possible (25).

Conclusions

Under the limits of the relatively limited group of cases, the data highlights certain etiological, therapeutic and outcomes peculiarities of this subcategory of patients that associate HNC with DM. This category of patients should not be treated differently even if a precaution is necessary due to the increased risk of complications related to treatment. Metformin could bring outcome benefit and the treatment of DM with insulin could be associated with a worst prognostic. The use of poly-chemotherapy regimens (platinum double or triple combination including platinum salts) demonstrates the feasibility of using chemotherapy for these subtype of patients. The tendency to de-escalate the treatment by omitting radiotherapy for this category of patients should also be noted. Neutrophil to lymphocyte ratio (NLR), a less specific biomarker could be less useful than the Glasgow Prognostic Score (GPS) which can be considered an accessible biomarker. A large percentage of sino-nasal cancers compared to the data reported in the literature could be also related to DM. Both, this possible association and the benefit of Metformin and 5-Flurouracil must be re-evaluated in studies in larger groups of patients. Poor glycemic control is identified in most cases of HNC with possible implications even in the corticosteroid management of acute toxicities.

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