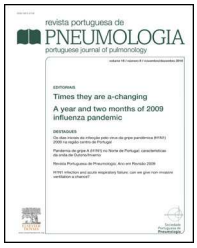
Rev Port Pneumol. 2014;20(2):57–59

revista portuguesa de
PNEUMOLOGIA
portuguese journal of pulmonology
www.revportpneumol.org



EDITORIAL

Diabetes mellitus as a prognostic factor in advanced non-small-cell lung cancer. To be or not to be: That is as *yet* an unsolved question☆

A diabetes *mellitus* como fator de prognóstico no carcinoma pulmonar de não pequenas células em estádio avançado. Ser ou não ser: Eis uma questão *ainda* não resolvida

There has been a marked increase in the prevalence of cancer and diabetes worldwide, with epidemiological evidence that diabetic patients present a significantly increased risk for certain malignancies, which does not seem to occur with lung cancer.[1,2] However, a meta-analysis of observational studies, recently published, puts forward the theory that diabetes *mellitus* (DM), independently and especially in women, could also increase the risk of lung cancer.[3]

Certain drugs used in the management of hyperglycaemia have, in turn, been linked to a greater or lesser risk of certain types of cancer, particularly lung cancer. Diabetics treated with metformin[4–7]or tiazolidinediones[4,8,9] are less likely to develop lung cancer – but there is no general agreement on this[10] –, as it has been pointed out that those who do suffer from this neoplasm can present a more aggressive phenotype of their disease when being treated with metformin.[4]

The prognostic factors for lung cancer have been exhaustively researched,[11.12] it is accepted that the classic ones are the anatomical stage of the tumour, *performance status* (PS) of the patient and the histological subtype of the neoplasm; also to be taken into account are the patient's gender, age, type of treatment, and many other clinical and biological parameters among which are included, most recently, some genetic and molecular characteristics of the tumour.[13,14]

Some doubts have been raised about the role of diabetes in the prognosis and mortality of lung cancer; there have been studies which have produced contradictory results in relation to these questions which up to now are still outstanding.[1,7,12,15–17]

The uncertainty which stems from this must be partly due to the heterogeneous nature of the studies analyzed, their design, the size of the population included, the weakness of the related statistics, the failure to include certain variables, the presence of confounding factors, and a number of other weaknesses which would be too long to list.

It is in this context that Inal et al.[18] carried out a retrospective study (442 patients with NSCLC in an advanced stage of the disease, including 66 diabetics), the results of which are published in this number of the Portuguese Journal of Pulmonology.[18] Their aim was to determine the prognostic value of some of the clinical characteristics of patients with advanced stage non-small cell lung cancer (NSCLC) who are being treated with platinum-based doublets – especially with reference to the impact of DM on the intervals of progression free survival (PFS) and global overall survival (OS).

In this study, various potential prognoses variables were analyzed, including DM, and it was observed, by univariate analysis, that for OS, PS, the stage of the disease, the presence of DM and liver or brain metastases were significant prognostic tools while for PFS only staging, the presence of DM or liver metastases were relevant.

From a multivariate analysis of results, a bad PS, the presence of DM and advanced stage were considered independent negative prognostic factors for OS, while DM and staging had the same significance in relation to PFS.

Given these findings, the authors conclude that DM, at the time of diagnosis, functions as a prognostic factor for PFS and OS, in patients with advanced stage NSCLC, under first line treatment with platinum-based doublets, and as

☆ Please cite this article as: Sotto-Mayor R. A diabetes *mellitus* como fator de prognóstico no carcinoma pulmonar de não pequenas células em estádio avançado. Ser ou não ser: Eis uma questão *ainda* não resolvida. Rev Port Pneumol. 2014;20:57–59.

with a poor PS, the advanced stage of the disease was also identified as a negative prognostic factor.

These results are not surprising in relation to the prognostic value which is traditionally attributed to the PS and the anatomical stage of NSCLC[11] but, in relation to DM, this role can be questioned given the small sample of patients analyzed, the fact that it is a retrospective study and that the diabetic population is not sufficiently well defined and stratified in terms of the duration of DM, the serum levels of glucose, the level of control and what treatment they are on, and sub-diagnoses could exist in what is considered the non-diabetic population, as the authors themselves acknowledge.[18]

Retrospective studies are extensively used in clinical research because they are less demanding and are based on data that are easily available, recorded in the clinical records of the patients, but their intrinsic value is dependent on the quality of those clinical records, from which important data may be missing, and there are other disadvantages such as the difficulty of controlling bias and confounding data – due to lack of randomization and to concealment –, so as to establish the relationship of cause and effect between the variables under consideration.[19]

Their results are, in the best-case scenario, generated by hypotheses, which should be confirmed by broader-based prospective studies which, by definition, would correspond to a higher level of scientific quality.[19]

Altogether, they have the virtue of functioning as pilot studies, contributing to a better definition of the questions raised, to establishing an appropriate size of sample and variables, to the identification of feasibility constraints, and also in aiding formulation and clarification of the hypotheses.[19]

The article published in the current issue,[18] apart from the assumptions mentioned, has the virtue of discussing the question of the possible prognostic significance of DM in patients with advanced stage NSCLC, responding to those who argue that its presence is accompanied by a worse prognosis of the cancer,[12,17] and it should be stressed that the authors propose, as would be expected,[19] new prospective studies, which are multi-centred, with a much bigger number of patients, to clear up the doubts that still persist in this area – whether DM as a prognostic factor is positive,[15] negative[12,17] or null.[16]

Inhibiting IGF-R1[20] (*insulin-like growth factor 1 receptor*) has been seen as a therapy for NSCLC at the metastatic stage, that is to say, particularly with a figitumab associated with conventional chemotherapy, but results achieved were negative in relation to OS and iatrogenicity, which includes serious diabetes in a significant percentage of cases,[21] leaving the question of whether, in the future, inhibition of this target therapy, with different drugs, could influence patient prognosis.

In the meantime, diabetic patients who require oncological treatment must receive rigorous and specialized care in order to control their hyperglycaemia, which has proved to allow for better results in antineoplastic therapy.[2]

Conflicts of interest

The author declares that there is no conflict of interest.

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