JACOBS PUBLISHERS

OPEN ACCESS

Jacobs Journal of Pulmonology

Observational Study

Effect of Metformin on Survival after Surgery for Non-small Cell Lung Cancer: Fiction or Fact?

Lisette T Hoekstra[1], Peter W Plaisier[1*], Eric van Thiel[2], Ronald AM Damhuis[3]

[1]*Department of Surgery, Albert Schweitzer Hospital Dordrecht, The Netherlands*

[2]*Department of Pulmonology, Albert Schweitzer Hospital, Dordrecht, The Netherlands*

[3]*Department of Registry and Research, Comprehensive Cancer Centre, Utrecht, the Netherlands*

**Corresponding author: Dr. P.W. Plaisier, Department of Surgery Albert Schweitzer Hospital, PO Box 444, NL-3300 AK Dordrecht, The Netherlands, Tel: +31 (0)78 6541111; Fax: +31 (0)78 6541736; E-mail: p.w.plaisier@asz.nl*

Received: 03-15-2016

Accepted: 04-25-2016

Published: 05-09-2016

Abstract

Objectives: Diabetes and metformin use have been suggested as prognostic factors in lung cancer. We studied the prognostic impact of metformin use in surgically treated lung cancer patients.

Methods: Patient and tumor characteristics, together with information on diabetes and diabetes medication were collected for stage I-II non-small cell lung cancer patients, treated by surgical resection in our hospital in the period 2003-2010. Groups were compared with chi-square analysis and differences in overall survival were tested with the log rank statistic. The independent value of prognostic factors was assessed in multivariate proportional hazard analysis.

Results: The final series comprised 138 men and 70 women, including 22 (11%) with diabetes. Within the latter group, 17 patients used metformin before diagnosis. Five-year survival was significantly better for metformin users than for non-diabetes patients: 84% against 46%, which difference remained significant after controlling for extent of surgery. Five-year survival for diabetes patients on other medication than metformin was 0%.

Conclusions: Our results suggest a positive effect on survival for metformin users undergoing lung cancer surgery. Metformin may, therefore, be considered a promising alternative for chemotherapy although our finding should be confirmed in larger series. Meanwhile, metformin use should be recorded in audit registries for lung cancer surgery.

Keywords: Metformin; Diabetes; NSCLC [Non-small cell Lung Cancer]; Lung Cancer; Survival

Introduction

During the last decade, several studies suggested that metformin, a common drug for the treatment of diabetes mellitus type 2, may reduce the risk of cancer and/or affect the prognosis. Effects of metformin have been reported for various types of cancer, such as oesophageal cancer [1], gastric cancer [2], oral squamous cell carcinoma [3], breast cancer [4], and ovarian cancer [5].

For lung cancer, reports regarding the influence of metformin have been ambiguous. In vivo research showed that metformin may prevent tobacco-induced cancer development [6]. An epidemiological study queried a database with health insurance claims to evaluate the lung cancer risk in diabetics and reported a risk reduction for metformin users [7]. More recently, a similar study [8] contradicted this finding and stated that most claims regarding metformin and cancer were caused by time-related bias. This type of methodological error is less likely for clinical studies and an observational study from Chi-

na [9] assessed survival for diabetes patients with advanced stage Non-Small Cell Lung Cancer (NSLC), treated with chemotherapy, and demonstrated a benefit for metformin users. In contrast, a recent case-control study from Cleveland [10] compared cancer phenotype and survival and reported that metformin users were more often diagnosed with metastatic disease and experienced poorer survival.

With respect to outcomes in lung cancer surgery in diabetics, pulmonary complications tend to be more common in obese patients but postoperative death and length of hospital of stay are not impaired [11]. In fact, high body mass index has even been mentioned as a beneficial factor for survival in patients operated for lung cancer [12]. The link between diabetes treatment and cancer progression is difficult to assess within clinical trials and observational research has been advocated [13]. Because information regarding the association between metformin and survival was lacking for surgical series, we decided to perform a retrospective study to determine the prognostic impact of metformin use in lung cancer patients primarily treated by surgery.

Patients and methods

A standard database of stage I-II NSCLC patients treated in the period 2003-2010 in the Albert Schweitzer Hospital Dordrecht was retrieved from the Netherlands Cancer Registry. This database contained information on age, gender, TNM stage, histotype and type of surgery. From this database we selected all patient treated by surgical resection. Patients with carcinoid tumours, sublobar resection, neoadjuvant chemotherapy, pN2/3 or residual disease were excluded from the study. Supplementary information on diabetes medication was collected from the medical files. Diabetes patients were stratified by type of treatment: metformin use (dailly 2-3 x 500-850mg; n=17) versus other medication (n=5). Patients developing diabetes around (n=4) or after diagnosis (n=8) were ignored.

Patient and tumour characteristics for the diabetes and metformin subgroups were tabulated and compared with the non-diabetes subgroup using chi-square analysis. Overall survival was calculated from day of surgery and differences between subgroups were tested for significance with the log rank statistic. The independent value of prognostic factors was assessed in multivariate proportional hazard analysis. Only factors with significant impact were maintained in the final model.

Results

The series comprised 208 patients, including 22 (11%) with diabetes. Within the latter group, 17 patients had been treated with metformin before diagnosis. After or around diagnosis, another 12 patients developed diabetes. The study base comprised 138 men and 70 women, with 45% of patients aged 70 years or older. Further patient characteristics are shown in Table 1. Adenocarcinoma comprised 45% of patients against 50% for squamous cell carcinoma and 5% for large cell carcinoma. FDG PET-scan was performed in 84% of patients and 27% were diagnosed with stage II. Stage I comprised 73% of cases. Lobectomy was performed in 87% of patients, including sleeve lobectomy in 11 patients. Bilobectomy and pneumonectomy were performed in 5% and 8% of patients, respectively. Adjuvant chemotherapy was administered in 12% (n=25), mainly in patients with stage II (23/25). Associations between diabetes, metformin use and other patient characteristics were not statistically significant. The diabetes subgroup comprised more adenocarcinoma (55% vs. 39%) and fewer patients younger than 60 years (5% vs. 24%).

		n	%	5-year survival	p
Gender	Men	138	67%	46	0.99
	Women	70	34%	50	
Age	20-59	46	22%	41	0.35
	60-69	68	33%	61	
	70-79	82	39%	45	
	80+	12	6%	35	
Period	2003-2006	101	49%	47	0.65
	2007-2010	107	51%	57	
Histotype	Adeno	85	41%	44	0.23
	Squamous	105	50%	50	
	Large	18	9%	44	
PET-scan	Yes	174	84%	50	0.48
	No	34	16%	40	
TNM stage	Ia	71	34%	50	0.01
	Ib	82	39%	56	
	IIa	14	7%	50	
	IIb	41	20%	30	
Procedure	Lobectomy	180	87%	50	0.004
	Bilobectomy	11	5%	72	
	Pneumonectomy	17	8%	11	
Adjuvant chemotherapy	Yes	25	12%	49	0.30
	No	183	88%	31	

Table 1. Patient characteristics.

Thirty-day postoperative mortality was 2.4%. Five-year survival was significantly better for metformin users, 84% against 46% for non-diabetes patients [Figure 1]. The survival difference remained significant (HR=0.24, p=0.048) after controlling

		Hazard ratio	95% Confidence Interval
Procedure	Lobectomy	1	-
	Bilobectomy	0.61	0.19-1.95
	Pneumonectomy	2.41	1.30-4.46
Diabetes	No	1	-
	Metformin	0.24	0.06-0.98
	Other treatment	3.01	1.09-8.32

Table 2. Prognostic factors according to multivariate analysis.

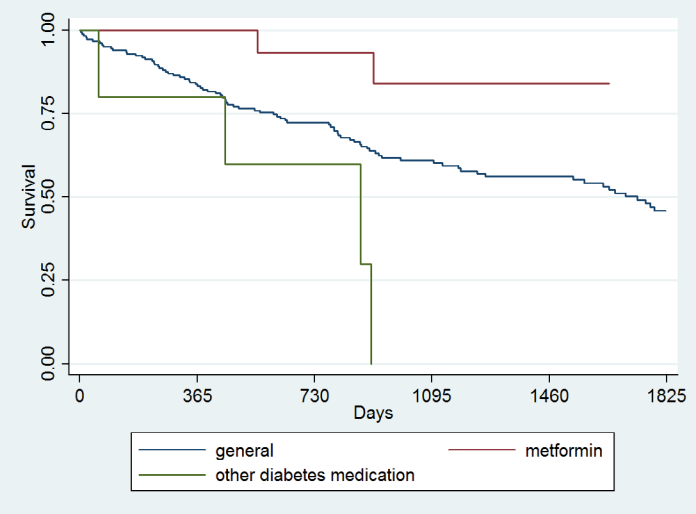

Figure 1. Survival stratified by diabetes medication.

for extent of surgery [Table 2].

Other factors had no independent prognostic impact. Two metformin users with squamous cell carcinoma died from recurrent cancer, but abdominal recurrences were not observed, refuting the theory regarding poor performance of PET-scans in metformin users. No deaths were observed among the metformin users with adenocarcinoma (n=9). Five-year survival for diabetes patients on other medication (n=5) was 0%.

Discussion

The results of this study suggest an association between metformin use before diagnosis and five year survival for patients who underwent surgery for stage I-II NSCLC. This kind of finding may be explained by chance, selection, unknown confounders or a true beneficial effect of metformin. Chance findings are common in observational research with small series and confirmation of our results in larger series is, therefore, demanded. Similar results from the united States were presented only recently [14, 15] and we are in the process of expanding our study to other hospitals in the Netherlands. Selection criteria for surgery may be stricter for patients with diabetes mellitus and the actual diabetes medication might depend on interaction with tumour load or micrometastases. It has been shown that the diagnosis of diabetes mellitus can be related to cancer diagnosis, generally referred to as reverse causation. Diabetes mellitus is often preceded by a long period of hyperglycaemia and hyperinsulinemia and cancer symptoms may trigger investigations leading to the diagnosis of diabetes. This phenomenon justifies our decision to ignore diagnosis of diabetes around or after cancer diagnosis. Another type of confounding may arise from excluding patients with higher stage or other treatments. Mazzone et al. [10] reported that metformin users tend to present with higher stage and experience poorer survival after non-surgical treatment. Future studies should incorporate the cancer phenotype of metformin users and determine the prognostic impact for the various subgroups, including stage, treatment and histotype to correct for these potential biases.

The possible true beneficial effect of metformin can be attributed to several mechanisms. An interaction between metformin use and chemotherapy is plausible given the high pathological complete response rates that were observed after neoadjuvant treatment for breast [16] and oesophageal cancer [17]. A recent study evaluated interaction with chemotherapy and reported that metformin increases the cytotoxic effect of chemotherapeutic agents, such as paclitaxel, by inhibition of p38 mitogen-activated protein kinase (MAPK) signalling [18]. Laboratory research, however, suggested that metformin may act directly at a cellular level as an inhibitor of the mechanistic target of rapamycin (mTOR), which is involved in cell metabolism and apoptosis [19].

Whether a true beneficial effect of metformin relates to treatment before or after diagnosis of lung cancer cannot be ascertained by our observational design. The exact mechanism explaining the impact of metformin on the occurrence and progression of cancer has also not yet been determined. Hyperglycaemia and hyperinsulinemia have been implicated in the proliferation of cancer cells and increased levels of Insulin Growth Factor 1 (IGF1) and overexpression of IGF1-receptor have been mentioned for several types of cancer [20]. Better control of glucose levels may explain variation in outcome between different types of diabetes treatment but does not clarify why metformin users have a better survival than non-diabetes patients. Signalling pathways have become an important target for recent lung cancer drugs and driver mutation analysis is increasingly performed to select the most appropriate intervention. Metformin, might interfere in these signalling pathways, yet the involved molecular mechanisms have not been fully elucidated. Laboratory research suggests that metformin may act directly at a cellular level as an inhibitor mTOR. It can also induce cytotoxicity by downregulating Thymidine Phosphorylase and ERCC1 expression [21]. In analogy, inactivation of tumour suppressor gene Liver Kinase B1 (LKB1) predicted apoptosis in NSCLC cell lines treated with phenformin [22], a

biguanide that is more potent than metformin but is no longer prescribed due to a high risk of fatal lactic acidosis. Judging from the biological complexity and the probable interaction between metformin, tumour characteristics and treatment options, further research will be required before embarking on randomized clinical trials. Whether a true beneficial effect of metformin relates to treatment before or after diagnosis of lung cancer cannot be ascertained by our observational design.

With respect to chemoprevention, the evidence regarding metformin and the incidence of lung cancer is still questionable. The observational studies are prone to bias and confounding and methodological error may explain a large part of the anti-cancer effects ascribed to metformin [23]. Several epidemiological studies examined lung cancer mortality as their main outcome measure but future studies should distinguish the individual effects on cancer incidence, phenotype at diagnosis and related survival.

Our study certainly has limitations. First of all, sample size is rather small as metformin use turned out to be lower than expected. However, the results for lung cancer mimic the metformin-related survival patterns for breast cancer [4]. The five-year survival for nondiabetic breast cancer patients was 82% versus 73% in the nonmetformin subgroup and 88% in the metformin subgroup. A survival advantage for metformin users was also reported for patients with stages I-III colorectal cancer [24]. For lung cancer, large multicentre studies are needed to confirm our finding and to assess whether the prognostic impact pertains to all histological subtypes and to patients treated by adjuvant chemotherapy. As a second limitation, survival was studied regardless of recurrence or cause of death and competing risks, especially those related to cardiovascular disease, tend to be more likely in patients with diabetes. Third, we did not evaluate glycaemic control through HbA1c levels or defined subclinical patients by examination of fasting blood glucose. Other limitations relate to the observational nature of this study, which was initially intended as a pilot project.[12]

In conclusion, our results suggest that overall survival for metformin users is better than for other surgically treated lung cancer patients. Before starting clinical trials, this finding needs to be confirmed in larger studies, including information on cancer phenotype, recurrence and cause of death. Metformin has a favorable toxicity compared to regular chemotherapy and should be considered as a promising agent for future adjuvant trials. In several countries, audit registries have been initiated to monitor the quality of lung cancer surgery. Comorbidity such as diabetes mellitus tends to be recorded, often including information on insulin-dependence. Our results suggest that metformin use should be added to the data dictionary of these registries.

Acknowledgement

This work has been presented earlier at the 21st European Conference on General Thoracic Surgeons, Birmingham, U.K.

Conflict of interest

none declared.

Take home message

We suggest a positive effect on survival for metformin users undergoing lung cancer surgery.

References

1. Kobayashi M, Kato K, Iwama H, Fujihara S, Nishiyama N et al. Antitumor effect of metformin in esophageal cancer: In vitro study. Int J Oncol. 2013, 42(2):517-524.

2. Kato K, Gong J, Iwama H, Kitanaka A, Tani J et al. The antidiabetic drug metformin inhibits gastric cancer cell proliferation in vitro and in vivo. Mol Cancer Ther. 2012, 11(3): 549-560.

3. Luo Q, Hu D, Hu S, Yan M, Sun Z et al. In vitro and in vivo anti-tumor effect of metformin as a novel therapeutic agent in human oral squamous cell carcinoma. BMC Cancer. 2012, 12: 517.

4. Hou G, Zhang S, Zhang X, Wang P, Hao X et al. Clinical pathological characteristics and prognostic analysis of 1,013 breast cancer patients with diabetes. Breast Cancer Res Treat. 2013, 137(3): 807-816.

5. Kumar S, Meuter A, Thapa P, Langstraat C, Giri S et al. Metformin intake is associated with better survival in ovarian cancer: A case-control study. Cancer. 2013; 119(3):555-562.

6. Memmott RM, Mercado JR, Maier CR, Kawabata S, Fox SD et al. Metformin prevents tobacco carcinogen--induced lung tumorigenesis. Cancer Prev Res. 2010, 3(9): 1066-1076.

7. Lai SW, Liao KF, Chen PC, Tsai PY, Hsieh DP et al. Antidiabetes drugs correlate with decreased risk of lung cancer: a population-based observation in Taiwan. Clin Lung Cancer. 2012, 13(2):143-148.

8. Smiechowski BB, Azoulay L, Yin H, Pollak MN, Suissa S. The use of metformin and the incidence of lung cancer in patients with type 2 diabetes. Diabetes Care. 2013, 36(1): 124-129.

9. Tan BX, Yao WX, Ge J, Peng XC, Du XB et al. Prognostic influence of metformin as first-line chemotherapy for advanced nonsmall cell lung cancer in patients with type 2 diabetes. Cancer. 2011, 117(2): 5103-5111.

10. Mazzone PJ, Rai H, Beukemann M, Xu M, Jain A et al. The effect of metformin and thiazolidinedione use on lung cancer in diabetics. BMC Cancer. 2012, 12:410.

11. Launer H, Nguyen DV, Cooke DT. National perioperative outcomes of pulmonary lobectomy for cancer in the obese patient: A propensity score matched analysis. J Thorac Cardiovasc Surg. 2013, 145(5): 1312-1318.

12. Attaran S, McShane J, Whittle I, Poullis M, Shackcloth M. A propensity-matched comparison of survival after lung resection in patients with a high versus low body mass index. Eur J Cardiothorac Surg. 2012, 42(4): 653-658.

13. Giovannucci E, Harlan DM, Archer MC, Bergenstal RM, Gapstur SM et al. Diabetes and cancer: a consensus report. Diabetes Care. 2010, 33(7): 1674–1685.

14. Fillon M. Cancer research at CHEST 2012 conference. J Natl Cancer Inst. 2013, 105(5): 311-312.

15. Dhilon SS, Groman A, Meagher A, Demmy T, Warren GW et al. Metformin and not diabetes influences the survival of resected early stage NSCLC patients. J Cancer Sci Ther. 2014, 6(7): 217-222.

16. Jiralerspong S, Palla SL, Giordano SH, Meric-Bernstam F, Liedtke C et al. Metformin and pathologic complete responses to neoadjuvant chemotherapy in diabetic patients with breast cancer. J Clin Oncol. 2009, 27(20): 3297-3302.

17. Skinner HD, McCurdy MR, Echeverria AE, Lin SH, Welsh JW et al. Metformin use and improved response to therapy in esophageal adenocarcinoma. Acta Oncol.2013, 52(5): 1002-1009.

18. Tseng SC, Huang YC, Chen HJ, Chiu HC, Huang YJ et al. Metformin-mediated downregulation of p38 mitogen-activated protein kinase-dependent excision repair cross-complementing 1 decreases DNA repair capacity and sensitizes human lung cancer cells to paclitaxel. Biochem Pharmacol. 2013, 85(4): 583-594.

19. Barrière G, Tartary M, Rigaud M. Metformin: a rising star to fight the epithelial mesenchymal transition in oncology. Anticancer Agents Med Chem. 2013, 13(2): 333-340.

20. Cohen DH, LeRoith D. Obesity, type 2 diabetes, and cancer: the insulin and IGF connection. Endocr Relat Cancer. 2012, 19(5): F27-45.

21. Ko JC, Huang YC, Chen HJ, Tseng SC, Chiu HC et al. Metformin Induces Cytotoxicity by Down-Regulating Thymidine Phosphorylase and ERCC1 Expression in Non-Small Cell Lung Cancer Cells. Basic Clin Pharmacol Toxicol. 2013, 113(1): 56-65.

22. Shackelford DB, Abt E, Gerken L, Vasquez DS, Seki A et al. LKB1 Inactivation Dictates Therapeutic Response of Non-Small Cell Lung Cancer to the Metabolism Drug Phenformin. Cancer Cell. 2013, 23(2):143-158

23. Suissa S, Azoulay L. Metformin and the risk of cancer: time-related biases in observational studies. Diabetes Care. 2012, 35(12): 2665-2673.

24. Garrett CR, Hassabo HM, Bhadkamkar NA, Wen S, Baladandayuthapani V et al. Survival advantage observed with the use of metformin in patients with type II diabetes and colorectal cancer. Br J Cancer. 2012, 106(8): 1374-1378.