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ScienceDirect

EJSO xx (2015) 1–7

EJSO the Journal of Cancer Surgery

www.ejso.com

Can metformin improve 'the tomorrow' of patients treated for oesophageal cancer?

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Accepted 15 May 2015

Available online ■ ■ ■

Abstract

Introduction: Recent studies suggest that the use of metformin is associated with reduced cancer incidence and improved prognosis in patients with oesophageal cancer. We explored the relationship between the use of metformin and outcome (pathologic response rate, distant metastasis-free and overall survival) in our mono-institutional cohort of patients treated for oesophageal cancer.

Material and methods: Between 2008 and 2014, a total of 196 patients with oesophageal cancer (ages ranged from 37 to 82 years) eligible for curative treatment entered the study. Patients were categorized as non-diabetic (n = 172), diabetic not taking metformin (n = 5) or diabetic taking metformin (n = 19). The majority of patients were treated with trimodality therapy (n = 189). Pathologic response was graded according to Mandard's tumour regression score at the time of surgery. Distant metastasis-free and overall survival were calculated using the Kaplan–Meier method with log rank comparisons performed to determine significance.

Results: The overall pathologic complete response rate for the study population was 26%. It was 25% for patients not using metformin and 39% for diabetics taking metformin (p = 0.260). The two-year overall survival rate for the whole group was 59%. Use of metformin was associated with a significantly better distant metastasis-free survival rate (p = 0.040) or overall survival rate (p = 0.012). Multivariate analysis using Cox regression found that metformin treatment significantly prolonged survival (p = 0.043).

Conclusion: In our population-based study, the use of metformin was associated with an improved overall and distant metastasis-free survival rate in patients with oesophageal cancer. These data are complementary to one other clinical study and warrant further prospective study.

Keywords: Oesophageal cancer; Diabetes; Metformin; Survival

Introduction

Oesophageal carcinoma is the eighth most common cancer worldwide and is known for its aggressive nature and poor survival rate.[1] Adenocarcinoma of the oesophagogastric junction (AEG) is increasingly common in the Western world and its prevalence now equals or surpasses that of squamous cell carcinoma (SCC).[2] Research has suggested that a high body mass index (BMI) is a major risk factor for the development of AEG.[3] The exact underlying pathomechanism is unclear, but over recent years chronic inflammation accompanying obesity has come to be seen as a crucial contributing factor.[4] The visceral adipose tissue is a sink of a high amount of systemically active cytokines and adipo-cytokines which act as pro-inflammatory mediators, initiating the metaplasia-dysplasia-adenocarcinoma sequence.[5] In addition to high BMI, type 2 diabetes has also become alarmingly common worldwide, sharing the same dual relationship with cancer incidence or mortality.[6]

Metformin (1,1-dimethylbiguanide hydrochloride) belongs to the biguanide class of oral antidiabetic drugs originally derived from galegine (isoamylene guanide), a

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http://dx.doi.org/10.1016/j.ejso.2015.05.012

0748-7983/

Please cite this article in press as: Van De Voorde L, et al., Can metformin improve 'the tomorrow' of patients treated for oesophageal cancer?, Eur J Surg Oncol (2015), http://dx.doi.org/10.1016/j.ejso.2015.05.012

guanidine derivative found in the French lilac Galega officinalis. This drug is typically used in the treatment of people with type 2 diabetes who also have obesity. Long-term use of this drug has been associated with reduced risks for some cancer types and improved cancer prognosis.[7–9]

At the molecular level, the exact mechanism for its anticancer effect is rather complicated and not fully clear. Encouraging results from preclinical data have indicated that metformin may prevent the development of oesophageal cancer.[10] Moreover, emerging clinical data suggests that cancer patients who take metformin have a better treatment response than those who do not.[11,12] Only one retrospective study has addressed the question of whether metformin, in conjunction with a standard neoadjuvant approach, could also improve complete remission and outcome in oesophageal cancer.[12] Therefore, the objective of this single-institution retrospective study was to investigate the effect of metformin on the outcomes in our oesophageal cancer patient cohort.

Material and methods

Patient selection

Two independent researchers reviewed clinical data about our patients who were treated with curative intent for oesophageal cancer between 2008 and 2014. A total of 196 patients met these criteria, of which 189 (96%) received neoadjuvant chemoradiotherapy (CRT). Only 7 (3%) had clinical stage cT1N0M0 disease and underwent primary surgical treatment.

All patients received initial staging with oesophagogastroscopy and biopsies, endoscopic ultrasound and positron emission tomography computed tomography (PET-CT). Staging was done in accordance with the American Joint Committee on Cancer TNM classification, 7th Edition. The standard neoadjuvant approach was to apply radiotherapy to the tumour and draining lymph nodes. Chemoradiotherapy consisted of 50.4 Gy combined with two cycles of cisplatin and 5-FU or 41.4 Gy combined with five cycles of carboplatin and paclitaxel.[13] All patients were treated with external beam radiation, using three-dimensional conformal radiation technique or Volumetric Modulated Arc Therapy (RapidArc). Re-evaluation with PET-CT was planned 6–8 weeks after CRT, followed by en-bloc-oesophagectomy with regional node dissection. Pathologic complete response (pCR) was defined as a tumour regression grade I based on the Mandard classification. In addition, the absence of tumour cells in sampled lymph nodes was necessary to fulfill the definition.

Patients were categorized as non-diabetic ($n = 172$), diabetic not taking metformin ($n = 5$) or diabetic taking metformin ($n = 19$). Classification of diabetes was based on pre-existing diagnosis prior to CRT. From the computer records, we identified all the patients' medical prescriptions. We also did an additional manual search of the patients' pharmacy records or charts to verify our data about the use of any anti-diabetic medications (metformin, sulfonylurea, alfa-glucosidase inhibitors, thiazolidinediones, meglitinides, dipeptidyl peptidase-4 inhibitors and insulin). We determined the cumulative daily use of metformin from prescription records found in electronic medical records or from self-reported records from the outpatient clinic. Pre-treatment height and weight were used to generate a pre-treatment BMI. Data were censored for analysis on 28 February 2015.

Statistics

All statistical analyses were conducted using SPSS (v.22). Univariate comparisons of patient characteristics between patients with or without metformin use were performed using a Pearson's Chi-square test for comparison of categorical data like sex or T stage and a Student's T-test for continuous data like age and BMI.

Pathologic complete response (pCR), overall survival (OS) and distant metastasis-free survival (DMFS) were the primary endpoints of this study. With respect to pCR, univariate analyses (either Pearson Chi-square or Student's T-test) were performed with the following variables: metformin use, age, BMI, tumour and nodal classification and histopathological subtype. Any variable with a significance of $p \leq 0.1$ was included in the multivariate analysis. Multivariate analysis was performed with logistic regression. All p-values for multivariate analysis are two-sided, with a $p < 0.05$ considered significant.

For DMFS and OS, time-to-event was calculated from the first day of radiation treatment or, when no neoadjuvant treatment was initiated, from the date of surgery until an event occurred or was censored. Event for DMFS was defined as recurrence of disease at distant sites or non-regional lymph nodes. These metastases were identified on computed tomography (with or without positron emission tomography) or chest X-ray. Pathologic confirmation of distant metastasis was not always available when evident. Event for OS was defined as death due to any cause. OS and DMFS were calculated using the Kaplan–Meier statistic, and log rank comparisons were performed to determine significance in univariate analyses for categorical predictors. Univariate analyses for continuous variables were performed using Cox proportional hazards regression. Any variable with a significance of $p \leq 0.1$ was included in the multivariate analysis. Multivariate analysis for DMFS and OS was performed with Cox proportional hazards regression. All p-values for multivariate analyses are two-sided, with a $p < 0.05$ considered significant.

Results

Patient and tumour characteristics

Of the 196 patients who were eligible for analysis, 10% ($n = 19$) had used metformin before and during their treatment. Detailed characteristics of cases and controls are

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