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Gastrointestinal Cancer

Impact of Metformin Use and Diabetic Status During Adjuvant Fluoropyrimidine-Oxaliplatin Chemotherapy on the Outcome of Patients with Resected Colon Cancer: A TOSCA Study Subanalysis

Claudio Vernieri,[a,b] Fabio Galli,[c] Laura Ferrari,[d] Paolo Marchetti,[e] Sara Lonardi,[f] Evaristo Maiello,[g] Rosario V. Iaffaioli,[h] Maria G. Zampino,[i] Alberto Zaniboni,[j] Sabino De Placido,[k] Maria Banzi,[l] Azzurra Damiani,[m] Daris Ferrari,[n] Gerardo Rosati,[o] Roberto F. Labianca,[p] Paolo Bidoli,[q] Giovanni L. Frassineti,[r] Mario Nicolini,[s] Lorenzo Pavesi,[t] Maria C. Tronconi,[u] Angela Buonadonna,[v] Sabrina Ferrario,[w] Giovanni Lo Re,[x] Vincenzo Adamo,[y] Emiliano Tamburini,[z] Mario Clerico,[aa] Paolo Giordani,[bb] Francesco Leonardi,[cc] Sandro Barni,[dd] Andrea Ciarlo,[ee] Luigi Cavanna,[ff] Stefania Gori,[gg] Saverio Cinieri,[hh] Marina Faedi,[ii] Massimo Aglietta,[jj] Maria Antista,[a] Katia F. Dotti,[a] Francesca Galli,[c] Maria Di Bartolomeo,[a] on behalf of TOSCA (Three or Six Colon Adjuvant) Investigators

[a]Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; [b]The Italian Foundation for Cancer Research Institute of Molecular Oncology, Milan, Italy; [c]IRCCS Istituto di Ricerche Farmacologiche Mario Negri, Milan, Italy; [d]Azienda Ospedaliero Universitaria Santa Maria della Misericordia, Udine, Italy; [e]Sant'Andrea Hospital, Sapienza University of Rome and IRCCS Istituto Dermopatico dell'Immacolata, Rome, Italy; [f]IRCCS Istituto Oncologico Veneto, Padua, Italy; [g]Ospedale Casa Sollievo della Sofferenza, San Giovanni Rotondo, Italy; [h]IRCCS Istituto Nazionale Tumori Fondazione G. Pascale, Naples, Italy; [i]IRCCS Istituto Europeo di Oncologia, Milan, Italy; [j]Fondazione Poliambulanza, Brescia, Italy; [k]Università Federico II, Naples, Italy; [l]IRCCS Arcispedale Santa Maria Nuova, Reggio Emilia, Italy; [m]IRCCS San Martino-IST, Genoa, Italy; [n]Azienda Ospedaliera San Paolo, Milan, Italy; [o]Ospedale San Carlo, Potenza, Italy; [p]ASST Papa Giovanni XXIII, Bergamo, Italy; [q]Ospedale San Gerardo dei Tintori, Monza, Italy; [r]IRCCS Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori, Meldola, Italy; [s]Azienda USL Romagna, Cattolica, Rimini, Italy; [t]Fondazione Salvatore Maugeri, Pavia, Italy; [u]Humanitas Clinical and Research Center, Rozzano, Milan, Italy; [v]Centro di Riferimento Oncologico, Aviano, Italy; [w]ASST Fatebenefratelli-Ospedale Luigi Sacco, Milan, Italy; [x]Azienda Ospedaliera S. Maria degli Angeli Pordenone, Pordenone, Italy; [y]Dipartimento Universitario di Patologia Umana & Azienda Ospedaliera Papardo, Messina, Italy; [z]Ospedale degli Infermi, Rimini, Italy; [aa]Ospedale degli Infermi, Biella, Italy; [bb]Ospedale San Salvatore, Pesaro, Italy; [cc]Azienda Ospedaliera Universitaria di Parma, Parma, Italy; [dd]Ospedale Treviglio Caravaggio Treviglio, Bergamo, Italy; [ee]USL4 Prato, Prato, Italy; [ff]Ospedale G. Da Saliceto, Piacenza, Italy; [gg]Ospedale Sacro Cuore Don Calabria, Verona, Italy; [hh]Presidio Ospedaliero Antonio Perrino, Brindisi, Italy; [ii]Presidio Ospedaliero Bufalini, Cesena, Italy; [jj]Istituto di Candiolo IRCC, Candiolo Torin, Italy

Disclosures of potential conflicts of interest may be found at the end of this article.

Abstract

Background. Type 2 diabetes mellitus (T2DM) is associated with increased risk of colon cancer (CC), whereas metformin use seems to be protective. However, the impact of metformin use on the risk of death or disease recurrence after radical surgery for CC remains uncertain.

Materials and Methods. This is a substudy conducted in patients with high-risk stage II or stage III CC randomized in the TOSCA trial, which compared 3 versus 6 months of fluoropyrimidine-oxaliplatin adjuvant chemotherapy. Objective of the study was to investigate the impact of metformin exposure during adjuvant chemotherapy on overall survival (OS) and relapse-free survival (RFS). We also evaluated the impact of T2DM or metformin dosage on clinical outcomes.

Results. Out of 3,759 patients enrolled in the TOSCA trial, 133 patients with diabetes (9.2%) and 1,319 without diabetes (90.8%) were recruited in this study. After excluding 13 patients with diabetes without information on metformin exposure, 76 patients with T2DM (63.3%) were defined as metformin users and 44 (36.7%) as metformin nonusers. After a median follow-up of 60.4 months, 26 (21.7%) patients relapsed and 16 (13.3%) died. Metformin use was neither associated with OS (adjusted hazard ratio [HR], 1.51; 95% confidence interval [CI], 0.48–4.77; p = .4781) nor with RFS (HR, 1.56; 95% CI, 0.69–3.54; p = .2881). Similarly, we found no association between T2DM or metformin dosage and OS or RFS.

Correspondence: Claudio Vernieri, M.D., Ph.D., Medical Oncology Department, Fondazione IRCCS Istituto Nazionale dei Tumori, Via G. Venezian, 1 20133, Milan, Italy. Telephone: 0039-02-23903066; e-mail: claudio.vernieri@istitutotumori.mi.it; or Maria Di Bartolomeo, M.D., Medical Oncology Department, Fondazione IRCCS Istituto Nazionale dei Tumori, Via G, Venezian, 1 20133, Milan, Italy. Telephone: 0039-02-23902882; e-mail: maria.dibartolomeo@istitutotumori.mi.it Received July 23, 2018; accepted for publication October 19, 2018; published Online First on January 3, 2019. http://dx.doi.org/10.1634/theoncologist.2018-0442

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Conclusions. Metformin use and T2DM did not impact on OS or RFS in patients with resected CC treated with adjuvant fluoropyrimidine-oxaliplatin chemotherapy. Larger studies and longer follow-up are required to clarify the potential efficacy of metformin in improving the prognosis of patients with CC. ***The Oncologist*** 2019;24:385–393

Implications for Practice: The role of the antidiabetic drug metformin in colon cancer prevention and treatment is highly debated. While low-dose metformin reduced the incidence of colorectal adenomas in two prospective studies, its effect in patients with already established colon cancer remains unclear. In this study, the potential impact of metformin on the survival of resected colon cancer patients who received adjuvant chemotherapy was investigated in the context of the TOSCA study. We did not find any association between metformin use or dosages and patient survival. Prospective studies are required to draw definitive conclusions about metformin impact on colon cancer recurrence and survival.

Introduction

In observational studies, hyperglycemia and diabetes have been associated with increased colorectal cancer incidence and mortality [1, 2]. Increased plasma glucose levels can sustain tumor cell bioenergetics and anabolic requirements, thus stimulating tumor growth and proliferation [3]. Moreover, type 2 diabetes mellitus (T2DM) is associated with insulin resistance and hyperinsulinemia, which can stimulate the insulin-like growth factor receptor 1-PI3K/AKT/mammalian target of rapamycin (mTOR) axis, a crucial orchestrator of cancer cell growth, proliferation, and survival [4, 5].

In recent years, the antidiabetic compound metformin has emerged as a promising antineoplastic drug in both preclinical and clinical studies [3, 6, 7]. Proposed mechanisms of metformin activity include (a) systemic metabolic effects, such as a reduction of plasma glucose and serum insulin/IGF-1 levels, and (b) cell autonomous antitumor effects resulting from impaired mitochondrial metabolism, activation of the AMP-activated protein kinase, and the consequent inhibition of mTOR and anabolic functions (i.e., fatty acid and cholesterol biosynthesis) in cancer cells [8]. In preclinical studies, metformin inhibited the growth of in vitro and in vivo models of colon cancer (CC) [9, 10] and also synergized with oxaliplatin [11]. In the clinical context, the role of metformin in CC prevention is supported by observational studies reporting on lower tumor incidence in patients with diabetes taking metformin [12] and also by two prospective interventional trials, in which low-dose metformin reduced the occurrence of colorectal adenomas in patients without diabetes [13, 14].

Conversely, the efficacy of metformin in reducing recurrences and/or improving survival in patients with resected CC is more uncertain. Although a recent meta-analysis showed an association between metformin use and better overall survival (OS) in patients with early-stage CC [15], the five studies included were highly heterogeneous in terms of design and patient characteristics; moreover, in two studies there was no evidence of a positive effect of metformin [16, 17]. Longer OS in metformin users could result from improved cancer-related outcomes or from the reduction of other causes of death in patients with diabetes, such as cardiovascular, cerebrovascular, or renal disease. The fact that metformin use has also been associated with better relapse-free survival (RFS) in some studies suggests an anti-CC activity [15].

The TOSCA trial is an open-label, phase III, multicenter noninferiority trial that randomized patients with high-risk stage II or stage III CC to receive 3 or 6 months of FOLFOX-4/CAPOX adjuvant chemotherapy (ChT). The trial failed to demonstrate a formal noninferiority of 3 months versus 6 months of treatment [18].

Based on available evidences, we hypothesized that metformin use in combination with adjuvant chemotherapy may be associated with better prognosis in patients with CC. In particular, we evaluated the association between metformin use and OS or RFS of patients with diabetes with CC enrolled in the TOSCA trial. As exploratory analyses, we also investigated the potential impact of diabetic status and metformin dosage on clinical outcomes.

Material and Methods

Study Population and Objectives of the Study

Our study was a preplanned analysis of the TOSCA population, although the participation in this subanalysis was not mandatory but at the discretion of each center. Main inclusion criteria were as follows: (a) histologically confirmed, high-risk stage II or stage III colon adenocarcinoma (high-risk stage II disease was defined as T4 stage; grade greater than or equal to 3; clinical presentation with bowel obstruction or perforation; histological evidence of vascular, lymphatic, or perineural invasion), (b) diagnosis of T2DM, (c) age ≥18 years, (d) Eastern Cooperative Oncology Group performance status (ECOG PS) ≤1, and (e) having undergone curative surgery no less than 3 and no more than 10 weeks prior to randomization.

Patients with diabetes were defined as patients with a diagnosis of T2DM at the time of enrollment in the study or during the course of adjuvant ChT. The diagnosis of T2DM had to be made by a physician specialist in diabetes management after excluding other causes of hyperglycemia or other diabetes types. Among patients with diabetes, we collected information on the use of antidiabetic therapies, including metformin and insulin. Metformin use and dosages were assessed at diabetes diagnosis, during ChT, and at the end of ChT. Patients were defined as metformin users if they took metformin at least during ChT, independently from its use in the pre- and/or post-ChT period.

The primary objective of this study was to investigate the impact of metformin use on patient OS, as defined as the time interval between randomization and death from any cause.

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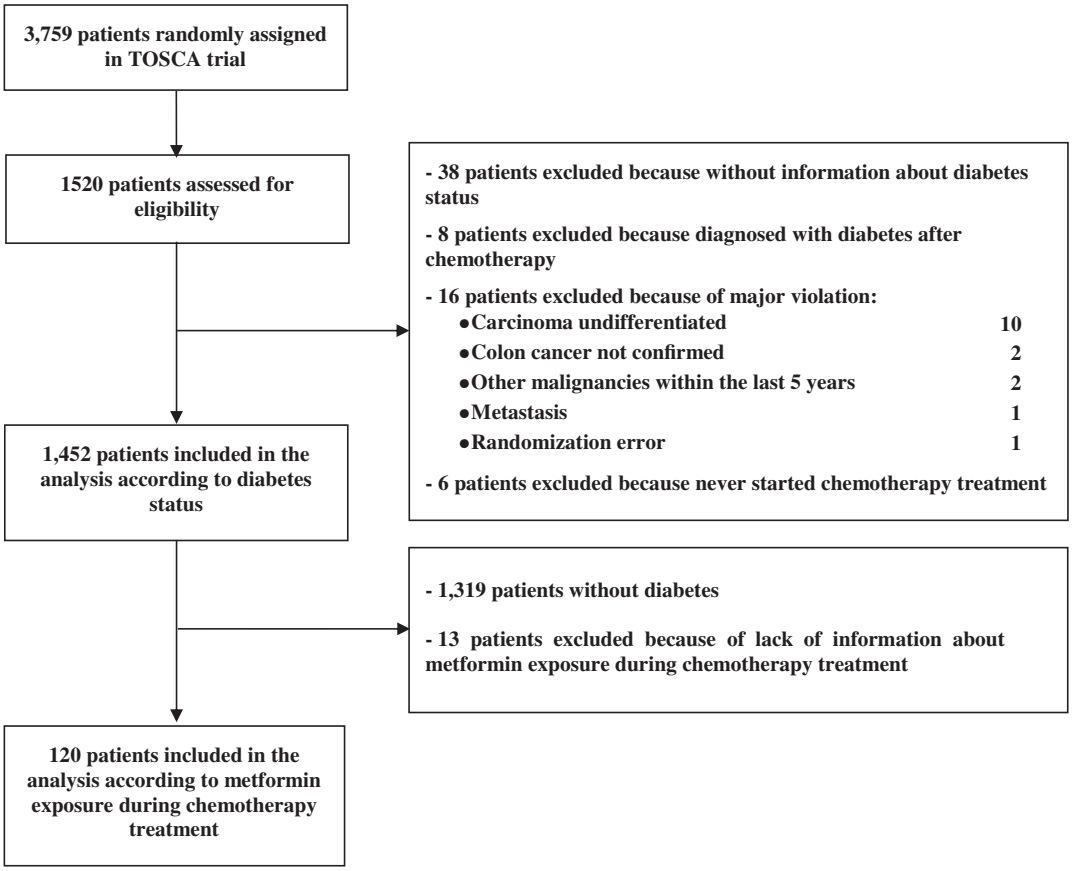

Figure 1. Study Flowchart.

Secondary objective was to study the association between metformin use and RFS, as defined as the time between randomization and disease relapse or death from any cause. Patients who had not relapsed or died while on study were censored at the date of the last disease assessment. Explorative analyses were performed to evaluate the impact of diabetic status or metformin dosage on OS and RFS.

Statistical Analysis

Sample size was calculated a priori based on an expected prevalence of T2DM of at least 11% in the whole TOSCA population. Assuming that 43% of patients with diabetes received metformin, a death rate of 43% (i.e., 173 deaths out of 413 patients) should be observed and a hazard ratio (HR) for OS of at least 0.65 associated with metformin administration, with a power of 80% and type-I error of 5% for bilateral test. Because 4 years of accrual and 3 years of follow-up were planned for the TOCA trial, the 43% death rate seemed reasonable by considering that a recently published randomized phase III trial reported a death rate of 34.1% after a median follow-up of 6.5 years in patients with diabetes with stage III CC [16].

The effect of metformin use and the impact of potential confounders on OS and RFS was explored by Cox proportional hazard models. Variables significantly associated with OS or RFS were included in a multivariable model to test their independent effect on clinical outcomes. Results of the analysis were expressed as HRs and 95% confidence intervals (CIs). Chi-square (or Fisher's exact test as appropriate) and Wilcoxon tests were performed to compare the distributions of categorical and continuous variable, respectively. Statistical significance was set at $p < .05$ for bilateral tests. Analysis was carried out using the SAS Version 9.4 (SAS Institute; Cary, NC) software.

Results

Patients' and Tumor Characteristics

Out of 3,759 patients enrolled in the TOSCA trial from 130 centers, 1,520 patients from 37 centers were assessed for eligibility in our study. 68 patients were excluded because of unavailability of information on diabetic status. Finally, 133 patients with T2DM and 1,319 patients without T2DM were included (Fig. 1). Patient and tumor characteristics are summarized in Table 1. Briefly, patients with diabetes were older than those without diabetes (67.5 vs. 63.6 years, $p < .0001$) and were more frequently obese (45.1% vs. 12.6%, $p < .0001$) or overweight (20.3% vs. 3.2%, $p < .0001$); moreover, there was a higher proportion of women among patients without diabetes than among patients with diabetes (47.5% vs. 38.3%; $p = .0446$). ECOG PS, tumor site, clinical stage, tumor grade, type (FOLFOX vs. XELOX), and duration (6 vs. 3 months) of adjuvant ChT did not significantly differ between patients with and without diabetes.

Among 133 patients with T2DM, data on metformin use were available for 120 patients, 76 of whom were metformin users and 44 were nonusers (Table 2). Metformin

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Table 1. Patient and tumor characteristics in patients with versus without diabetes

Characteristics	No diabetes (*n* = 1,319), *n* (%)	Diabetes (*n* = 133), *n* (%)	Overall (*n* = 1,452), *n* (%)	Wilcoxon or chi-square *p* value
Median age (Q1–Q3)	63.6 (56.5–70.0)	67.5 (62.5–72.2)	64.0 (57.0–70.4)	
Female sex	626 (47.5)	51 (38.3)	677 (46.6)	.0446
Performance status				
0	1,250 (94.8)	121 (91.0)	1,371 (94.4)	.0694
1	69 (5.2)	12 (9.0.0)	81 (5.6)	
Tumor site				.1315
Right sides	506 (38.4)	57 (42.9)	563 (38.9)	
Left sides	766 (58.2)	68 (51.1)	834 (57.6)	
Multiple site	44 (3.3)	8 (6.0)	52 (3.6)	
Missing	3	0	3	
T stage				
Tx	6 (0.5)	0 (0.0)	6 (0.4)	
T1	30 (2.3)	2 (1.5)	32 (2.2)	
T2a	62 (4.7)	13 (9.8)	75 (5.2)	
T2b	40 (3.0)	4 (3.0)	44 (3.0)	
T3	982 (74.8)	97 (72.9)	1,079 (74.7)	
T4	192 (14.6)	17 (12.8)	209 (14.5)	
Missing	7	0	7	
N stage				
Nx	3 (0.2)	0 (0.0)	3 (0.2)	
N0	450 (34.3)	45 (33.8)	495 (34.2)	
N1	640 (48.7)	69 (51.9)	709 (49.0)	
N2	220 (16.8)	19 (14.3)	239 (16.5)	
Missing	6	0	6	
Clinical stage				.8647
II	456 (34.6)	45 (33.8)	501 (34.5)	
III	863 (65.4)	88 (66.2)	951 (65.5)	
Grade				.7032
GX	7 (0.5)	0 (0.0)	7 (0.5)	
G1	85 (6.5)	11 (8.5)	96 (6.7)	
G2	791 (60.9)	77 (59.7)	868 (60.8)	
G3	415 (32.0)	41 (31.8)	456 (32.0)	
Missing	21	4	25	
Chemotherapy regimen				.7783
FOLFOX-4 (6 months)	384 (29.1)	38 (28.6)	422 (29.1)	
XELOX (24 weeks)	292 (22.1)	25 (18.8)	317 (21.8)	
FOLFOX-4 (3 months)	361 (27.4)	38 (28.6)	399 (27.5)	
XELOX (12 weeks)	282 (21.4)	32 (24.1)	314 (21.6)	
BMI categorization				<.0001
Underweight	888 (67.3)	8 (6.0)	896 (61.7)	
Normal	223 (16.9)	38 (28.6)	261 (18.0)	
Overweight	166 (12.6)	60 (45.1)	226 (15.6)	
Obese	42 (3.2)	27 (20.3)	69 (4.8)	

Abbreviation: BMI, body mass index.

users were less likely to be women (34.2% vs. 47.7%) and more likely to have left-sided tumors (59.2% vs. 38.6%). Details on metformin exposure are summarized in supplemental online Table 1.

Impact of Metformin Use on Clinical Outcomes in Patients with Diabetes

During a median follow-up of 60.3 months, 26 (21.7%) patients with T2DM relapsed, 16 (13.3%) patients died, and

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Table 2. Patient and tumor characteristics in metformin users versus nonuser

Characteristics	No metformin (*n* = 44), *n* (%)	Metformin (*n* = 76), *n* (%)	Overall (*n* = 120), *n* (%)	Wilcoxon or chi-square *p* value
Median age (Q1–Q3)	67.9 (65.5–72.2)	67.2 (62.0–72.5)	67.4 (62.5–72.3)	
Female sex	21 (47.7)	26 (34.2)	47 (39.2)	.1438
Performance status				
0	40 (90.9)	70 (92.1)	110 (91.7)	1.0000[a]
1	4 (9.1)	6 (7.9)	10 (8.3)	
Tumor site				.0734[a]
Right sides	25 (56.8)	27 (35.5)	52 (43.3)	
Left sides	17 (38.6)	45 (59.2)	62 (51.7)	
Multiple site	2 (4.5)	4 (5.3)	6 (5.0)	
T stage				
T1	0 (0.0)	2 (2.6)	2 (1.7)	
T2a	5 (11.4)	8 (10.5)	13 (10.8)	
T2b	0 (0.0)	3 (3.9)	3 (2.5)	
T3	33 (75.0)	53 (69.7)	86 (71.7)	
T4	6 (13.6)	10 (13.2)	16 (13.3)	
N stage				
N0	16 (36.4)	22 (28.9)	38 (31.7)	
N1	21 (47.7)	43 (56.6)	64 (53.3)	
N2	7 (15.9)	11 (14.5)	18 (15.0)	
Clinical stage				.4000
II	16 (36.4)	22 (28.9)	38 (31.7)	
III	28 (63.6)	54 (71.1)	82 (68.3)	
Grade				.1886
G1	4 (9.5)	6 (8.1)	10 (8.6)	
G2	29 (69.0)	40 (54.1)	69 (59.5)	
G3	9 (21.4)	28 (37.8)	37 (31.9)	
Missing	2	2	4	
Chemotherapy regimen				.4069
FOLFOX-4 (6 months)	14 (31.8)	18 (23.7)	32 (26.7)	
XELOX (24 weeks)	8 (18.2)	16 (21.1)	24 (20.0)	
FOLFOX-4 (3 months)	9 (20.5)	25 (32.9)	34 (28.3)	
XELOX (12 weeks)	13 (29.5)	17 (22.4)	30 (25.0)	
BMI categorization				.4069
Underweight	2 (4.5)	5 (6.6)	7 (5.8)	
Normal	15 (34.1)	20 (26.3)	35 (29.2)	
Overweight	19 (43.2)	34 (44.7)	53 (44.2)	
Obese	8 (18.2)	17 (22.4)	25 (20.8)	

[a]Fisher's test *p* value.
Abbreviation: BMI, body mass index.

29 (24.2%) patients relapsed and/or died. Metformin exposure was associated neither with OS (adjusted HR [aHR], 1.51; 95% CI, 0.48–4.77; $p = .4781$; Table 3A) nor with RFS (HR, 1.56; 95% CI, 0.69–3.54; $p = .2881$; Table 3B). At univariable analysis, shorter duration of adjuvant ChT (3 vs. 6 months) was associated with worse lower OS, but this association was not confirmed at multivariable analysis.

Although the HR of RFS for patients receiving 3 months versus 6 months of adjuvant ChT was equal to 2.27, this association did not meet statistical significance ($p = .0502$). Because no significant impact of other variables on RFS was detected, we did not perform multivariable analysis.

Exploratory Analysis on Impact of Diabetes on Clinical Outcomes

During a median follow-up of 62.3 months, 243 (16.7%) patients relapsed, 162 (11.2%) died, and 287 (19.8%) relapsed and/or died. We found no effect of T2DM on OS after adjusting for other covariates (aHR, 0.80; 95% CI, 0.47–1.37; $p = .4120$; Table 4A). At both univariable and

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Table 3. Effect of metformin exposure on overall survival **(A)** or relapse-free survival **(B)** in diabetic patients. Univariable and multivariable Cox proportional hazard models

A				
	Univariable analysis		Multivariable analysis	
	Covariate hazard ratio (95% CI)	*p* value	Hazard ratio (95% CI)	*p* value
Metformin exposure	1.69 (0.54–5.30)	.3696	1.51 (0.48–4.77)	.4781
Treatment duration: 3 mo/24 wk vs. 6 mo/12 wk	3.66 (1.03–12.98)	.0446	3.53 (0.99–12.55)	.0515
Age (1 yr increase)	0.98 (0.91–1.06)	.6323		
Female sex	0.74 (0.25–2.17)	.5831		
BMI equal or higher than 25	1.38 (0.44–4.35)	.5772		
ECOG performance status = 1 (vs. 0)	0.89 (0.12–6.75)	.9083		
Clinical stage III (vs. II)	1.24 (0.40–3.90)	.7110		
Grade (increase of 1)	1.59 (0.61–4.12)	.3442		
B				
	Univariable analysis		Multivariable analysis	
	Covariate hazard ratio (95% CI)	*p* value	Hazard ratio (95% CI)	*p* value
Metformin exposure	1.56 (0.69–3.54)	.2881	Multivariable analysis not performed	
Treatment duration: 3 mo/24 ws vs. 6 mo/12 wk	2.27 (1.00–5.15)	.0502		
Age (1 yr increase)	0.98 (0.93–1.04)	.5873		
Female sex	0.80 (0.37–1.72)	.5623		
BMI equal or higher than 25	1.06 (0.48–2.35)	.8804		
ECOG performance status = 1 (vs. 0)	0.94 (0.22–3.95)	.9297		
Clinical stage III (vs. II)	1.34 (0.57–3.15)	.5020		
Grade (increase of 1)	1.29 (0.66–2.52)	.4498		
Tumor site (ref. right)		.6314		
Left	0.72 (0.34–1.54)	.3970		
Multiple site	0.54 (0.07–4.11)	.5522		

Note: Tumor site was not included in the analysis because there are no events for the category "Multiple site."
Abbreviations: BMI, body mass index; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group.

multivariable analysis, older age, worse ECOG PS (1 vs. 0), and stage III (vs. II) correlated with shorter OS, whereas left-sided tumors were associated with better OS. Similarly, T2DM did not impact on RFS after adjusting for age, ECOG PS, and stage (aHR, 1.07; 95% CI, 0.73–1.55; p = .7378). Older age, worse ECOG PS (1 vs. 0), and stage III (vs. II) were associated with shorter RFS at both univariable and multivariable analysis (Table 4B).

Exploratory Analysis on Metformin Dosage

Data on metformin dosages were available for 95 patients. Overall, 22 (23.2%) patients relapsed, 13 (13.7%) patients died, and 24 (23.3%) patients relapsed and/or died. After adjusting for ChT duration, we did not find a significant association between metformin dosages and OS (aHR for 100 mg increase, 1.74; 95% CI, 0.54–5.67; p = .3555) or RFS (aHR, 1.03; 95% CI, 0.98–1.08; p = .2680; data not shown).

Discussion

Although metformin seems to reduce the incidence of preneoplastic lesions in the colon (polyps, adenomas) of patients without diabetes as well, its impact on the prognosis of patients with already established CC remains uncertain. In this study we evaluated the impact of metformin use in patients with resected CC enrolled in the TOSCA trial. We found no significant association between metformin use and the survival of patients with diabetes with resected high-risk stage II or stage III CC who received FOLFOX-4/XELOX adjuvant ChT.

Our results are in contrast with the conclusions of a recent meta-analysis of five studies, which demonstrated a significantly lower risk of death in metformin users compared with nonusers [15]. However, studies included in this meta-analysis were highly heterogeneous in terms of design, number of patients evaluated, and inclusion criteria; moreover, in two of these studies, OS was not significantly different between metformin users and nonusers [16, 17], whereas only one study showed remarkably better OS in metformin users [19].

Different hypotheses can explain the negative results of our study: (a) the lack of a real antitumor effect of metformin against CC, (b) the type of ChT used, and (c) an insufficient number of death/relapse events.

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Table 4. Effect of diabetic status on overall survival **(A)** or relapse-free survival **(B)**. Univariable and multivariable Cox proportional hazard models

A				
	Univariable analysis		Multivariable analysis	
	Covariate hazard ratio (95% CI)	*p* value	Hazard ratio (95% CI)	*p* value
Diabetes	1.07 (0.63–1.83)	.7944	0.80 (0.47–1.37)	.4120
Treatment duration: 3 mo/24 wk vs. 6 mo/12 wk	1.07 (0.78–1.46)	.6774		
Age (1 yr increase)	1.06 (1.04–1.08)	<.0001	1.05 (1.03–1.07)	<.0001
Female sex	0.95 (0.70–1.31)	.7725		
BMI equal or higher than 25	0.78 (0.52– 1.18)	.2399		
ECOG performance status = 1 (vs. 0)	2.88 (1.80–4.60)	<.0001	2.28 (1.41–3.68)	.0008
Clinical stage III (vs. II)	1.65 (1.15–2.37)	.0066	1.57 (1.09–2.26)	.0149
Grade (increase of 1)	1.28 (0.97–1.71)	.0855		
Tumor site (ref. right)		<.0001		.0003
Left	0.47 (0.34–0.65)	<.0001	0.51 (0.37–0.71)	<.0001
Multiple site	0.77 (0.34–1.76)	.5323	0.68 (0.30–1.57)	.3713
B				
	Univariable analysis		Multivariable analysis	
	Covariate hazard ratio (95% CI)	*p* value	Hazard ratio (95% CI)	*p* value
Diabetes	1.24 (0.86–1.80)	.2543	1.07 (0.73–1.55)	.7378
Treatment duration: 3 mo/24 wk vs. 6 mo/12 wk	1.11 (0.88–1.40)	.3641		
Age (1 yr increase)	1.03 (1.02–1.04)	<.0001	1.03 (1.01–1.04)	.0001
Female sex	0.99 (0.78–1.25)	.9296		
BMI equal or higher than 25	0.82 (0.61– 1.11)	.1966		
ECOG performance status = 1 (vs. 0)	2.09 (1.42–3.09)	.0002	1.84 (1.24–2.73)	.0025
Clinical stage III (vs. II)	1.66 (1.27–2.16)	.0002	1.59 (1.21–2.08)	.0007
Grade (increase of 1)	1.18 (0.96–1.46)	.1235		
Tumor site (ref. right)		.0982		
Left	0.77 (0.61–0.98)	.0314		
Multiple site	0.84 (0.44–1.60)	.6015		

Abbreviations: BMI, body mass index; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group.

Regarding the first hypothesis, metformin displays in vitro antitumor effects at concentrations that are in the order of millimolars (i.e. by far superior to those that can be safely reached in the blood of patients with diabetes, in the order of nanomolars) [10]. Although metformin dosages commonly used for T2DM treatment are active in more precocious phases of CC tumorigenesis [13, 14], they could be ineffective in inhibiting the growth or preventing recurrences of already established neoplasms. In retrospective studies, a dose-response relationship is one of the strongest arguments in favor of a possible anticancer effect of metformin [20]. In our study, metformin dosages were not associated with OS or RFS. However, the low number of patients and death/relapse events limits the possibility to draw definitive conclusions.

As for the second hypothesis, a potential antitumor effect of metformin may have been masked by the fact that all patients in the TOSCA trial received highly oxaliplatin-fuoropyrimidine ChT, which may provide the highest protection against CC recurrences. Conversely, metformin could add antitumor efficacy to ChT regimens containing only fuoropyrimidines. Our findings are consistent with results reported by Singh et al., who did not find a significant association between metformin use and the OS or RFS of patients with stage III CC receiving FOLFOX plus/minus cetuximab adjuvant ChT [16]. Our analysis and the study by Singh et al. are the only two studies that explored the impact of metformin in a homogeneous cohort of patients with stage II–III CC treated in the context of phase III randomized trials. In contrast, those studies that found an impact of metformin on better outcome considered patients with CC with stage I to IV disease, and treated with different types of ChT regimens, including patients with low-stage cancers who did not receive ChT and patients with advanced disease receiving multiple treatment lines [19–21]. Although the effect of metformin on clinical outcomes was balanced for tumor stage, the type of ChT was not considered as a potential confounder, thus precluding the possibility to test our hypothesis [21].

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The third hypothesis is related the low number of patients included and clinical events (death/relapse) observed. Unfortunately, only 37 out of 130 centers involved in the TOSCA trial took part in this substudy. Moreover, there was a much lower than expected frequency of death events in the population of patients with diabetes (13.3 vs. 43%), which was unexpected, especially if we consider that the study by Singh et al. reported a 34.1% death rate after 6.5 years of follow-up in patients with diabetes with stage III CC cancer receiving oxaliplatin-containing ChT. These factors have probably precluded the possibility of finding small OS differences between metformin users and nonusers.

One possible explanation for the discordant results among different studies is the definition of "metformin users." In most published studies, they were defined as patients taking metformin at ChT initiation or within 1 year before ChT [16]. In our study, metformin users took metformin at least during the whole course of adjuvant ChT, independently from its use before and/or after ChT; this definition is based on the hypothesis of a synergistic anticancer activity between metformin and fluoropyrimidines plus oxaliplatin [11, 22]. Despite these discrepancies, results of our analysis were confirmed when we considered as metformin users those patients taking metformin before ChT initiation (not shown); these results make our findings comparable with those of previous studies.

We also failed to demonstrate an association between diabetes mellitus and RFS or OS. This result contradicts the findings of recent meta-analyses of observational studies, which demonstrated an increased risk of death in patients with versus without diabetes with resected CRC [23, 24]. However, our study was not powered to test the hypothesis of reduced OS or RFS in patients with diabetes. Moreover, published studies are characterized by remarkable heterogeneity in statistical design and type of patients included (e.g., disease stages, type of treatment administered). Finally, differences in the time of diabetes diagnosis (e.g., before, during, or after adjuvant chemotherapy) between different analyses may in part explain the apparently contrasting findings.

Strengths of this study consist of its prospective design, a priori calculation of sample size, preplanned evaluation of glycemic status and metformin use, and a relatively homogeneous cohort of patients included in a phase III, randomized trial. Limitations consist of the lower than expected number of patients included and short follow-up period, with consequently low number of relapse and death events. Because adequate follow-up duration is important to reliably assess the potential role of metformin in affecting cancer recurrence, these limitations may have contributed to the negative findings of our study [15].

Conclusion

The impact of metformin on OS and RFS in patients with resected CC remains uncertain. Larger prospective studies in homogeneous patient populations—possibly in the context of randomized phase III trials to guarantee regular follow-up and data collection—and longer follow-up are necessary to clarify the role of metformin in preventing CC recurrence and death.

Author Contributions

Conception/design: Claudio Vernieri, Fabio Galli, Maria Di Bartolomeo

Provision of study material or patients: Claudio Vernieri, Fabio Galli, Laura Ferrari, Paolo Marchetti, Sara Lonardi, Evaristo Maiello, Rosario V. Iaffaioli, Maria G. Zampino, Alberto Zaniboni, Sabino De Placido, Maria Banzi, Azzurra Damiani, Daris Ferrari, Gerardo Rosati, Roberto F. Labianca, Paolo Bidoli, Giovanni L. Frassineti, Mario Nicolini, Lorenzo Pavesi, Maria C. Tronconi, Angela Buonadonna, Sabrina Ferrario, Giovanni Lo Re, Vincenzo Adamo, Emiliano Tamburini, Mario Clerico, Paolo Giordani, Francesco Leonardi, Sandro Barni, Andrea Ciarlo, Luigi Cavanna, Stefania Gori, Saverio Cinieri, Marina Faedi, Massimo Aglietta, Maria Antista, Katia F. Dottif, Francesca Galli, Maria Di Bartolomeo

Collection and/or assembly of data: Claudio Vernieri, Fabio Galli, Katia F. Dotti, Francesca Galli, Maria Di Bartolomeo

Data analysis and interpretation: Claudio Vernieri, Fabio Galli, Francesca Galli, Maria Di Bartolomeo

Manuscript writing: Claudio Vernieri, Fabio Galli, Maria Di Bartolomeo

Final approval of manuscript: Claudio Vernieri, Fabio Galli, Laura Ferrari, Paolo Marchetti, Sara Lonardi, Evaristo Maiello, Rosario V. Iaffaioli, Maria G. Zampino, Alberto Zaniboni, Sabino De Placido, Maria Banzi, Azzurra Damiani, Daris Ferrari, Gerardo Rosati, Roberto F. Labianca, Paolo Bidoli, Giovanni L. Frassineti, Mario Nicolini, Lorenzo Pavesi, Maria C. Tronconi, Angela Buonadonna, Sabrina Ferrario, Giovanni Lo Re, Vincenzo Adamo, Emiliano Tamburini, Mario Clerico, Paolo Giordani, Francesco Leonardi, Sandro Barni, Andrea Ciarlo, Luigi Cavanna, Stefania Gori, Saverio Cinieri, Marina Faedi, Massimo Aglietta, Maria Antista, Katia F. Dottif, Francesca Galli, Maria Di Bartolomeo

Disclosures

The authors indicated no financial relationships.

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For Further Reading:
Preet Paul Singh, Qian Shi, Nathan R. Foster et al. Relationship Between Metformin Use and Recurrence and Survival in Patients With Resected Stage III Colon Cancer Receiving Adjuvant Chemotherapy: Results From North Central Cancer Treatment Group N0147 (Alliance). ***The Oncologist*** 2016;21:1509–1521.

Implications for Practice:
The present study did not find any relationship between metformin use or its duration and disease-free survival, time to recurrence, and overall survival in a large cohort of patients with resected stage III colon cancer receiving adjuvant FOLFOX (folinic acid, fluorouracil, oxaliplatin)-based chemotherapy. This relationship was not modified by KRAS or BRAF mutation or DNA mismatch repair status. Metformin use did not increase or decrease the likelihood of chemotherapy-related grade 3 or higher adverse events.