RESEARCH ARTICLE

Metformin Addition to Chemotherapy in Stage IV Non-Small Cell Lung Cancer: an Open Label Randomized Controlled Study

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Abstract

Purpose: To evaluate effects of metformin on clinical outcome of non-diabetic patients with stage IV NSCLC. Materials and Methods: A prospective, randomized, open-label, controlled pilot study was conducted on patients with stage IV NSCLC with an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0-2, excluding patients with diabetes and lactic acidosis. Thirty chemo-naïve, non-diabetic patients with stage IV NSCLC were enrolled. Fifteen patients received intravenous gemcitabine/cisplatin regimen alone (arm B) while fifteen patients received the same regimen plus daily oral metformin 500mg (arm A). The effect of metformin on chemotherapy-response rates, survival, and adverse events in these patients was evaluated. Results: Objective response rate (ORR) and median overall survival (OS) in arms A and B were 46.7% versus 13.3% respectively, p=0.109 and 12 months versus 6.5 months, respectively, p=0.119. Median progression free survival (PFS) in arms A and B was 5.5 months versus 5 months, p=0.062. No significant increase in toxicity was observed in arm A versus arm B. Percentage of patients who experienced nausea was significantly lower in arm A versus arm B, at 26.7% versus 66.7% respectively, p=0.028. Conclusions: Metformin administration reduced occurrence of chemotherapy induced-nausea. Non-statistically significant improvements in the ORR or OS were observed. Metformin had no effect on PFS.

Keywords: Metformin - lung cancer - survival - mTOR - non-small cell

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Introduction

The prognosis of lung cancer patients remains dismal, most people afflicted with advanced stages will die of the disease, with the five-year survival rate being at the best 15% (Klastersky and Awada, 2012). Platinum based doublets are the standard first line chemotherapy for patients with advanced NSCLC, with about one-third of patients obtaining an objective response and another 20-30% achieving temporary disease stabilization. However, all patients inevitably experience disease progression (Xiao et al., 2013). Treatment with conventional chemotherapy for advanced NSCLC has reached a therapeutic plateau with a median survival time of 10 to 12 months. Thus, the need for new therapeutic opportunities is huge, and the introduction of targeted therapies for specific groups of patients has already demonstrated a great promise. One of the promising targets identified is the mammalian target of rapamycin (mTOR), which was found to be activated in a substantial number of lung cancer cases (Han et al., 2013; Tan et al., 2014).

Metformin (1,1-dimethylbiguanide hydrochloride) is a biguanide derivative that has been long used for treating diabetes mellitus (Witters, 2001). With an indirect mTOR inhibitor effect, Metformin might play a role as part of anti-cancer regimens, especially in tumors which are resistant to chemotherapy (Micic et al., 2011; Aljada and Mousa, 2012; Bost et al., 2012). Preclinical evidence supported the use of Metformin in chemoprevention of tobacco induced tumorgenesis in lungs of mice (Memmott et al., 2010). However, several population and institutional based epidemiological studies that examined the impact of Metformin use on lung cancer incidence produced conflicting results (Evans et al., 2005; Mazzone et al., 2012; Wang et al., 2013; Nie et al., 2014). The effect of Metformin as a cancer therapeutic was demonstrated by several observational studies (Jiralerspong et al., 2009; Tan et al., 2011; Zhang and Li, 2014). This potentially beneficial effect was further supported by preclinical studies showing a synergistic anti-proliferative effect of Metformin with different chemotherapeutic agents in NSCLC cell lines (Ashinuma et al., 2012; Bradford and Khan, 2013). The aim of this study was to evaluate the safety and efficacy of the addition of Metformin to first line chemotherapy regimen Gemcitabine and Cisplatin in chemo-naive stage IV metastatic NSCLC patients.

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Materials and Methods

Study design and participants

The study was a prospective, randomized, open-label, controlled pilot study. Eligible patients were aged 18-80 years and had newly diagnosed, chemo-naive, stage IV NSCLC determined by clinical, radiological and pathologic criteria that could be measured or assessed, or both. Furthermore, patients had to have an ECOG PS of 0-2. Additional inclusion criteria were absolute neutrophil count of more than 1.5×10^9 cells per L, more than 100×10^9 platelets per L, conjugated bilirubin serum concentration of up to 1.5 times the upper limit of normal, serum concentrations of alkaline phosphatase and aminotransferases of up to 2.5 times the upper limit of normal, and creatinine clearance of more than 60 mL/min. Patients were excluded if they had diabetes mellitus, history of lactic acidosis, allergy to Metformin or patients with comorbid diseases such as congestive heart failure, or chronic lung disease with hypoxia.

All 30 eligible patients were stratified according to gender and randomly assigned by permuted-block randomization to either arm A or arm B. Arm A (Metformin arm): 15 patients received the Gemcitabine/ Cisplatin regimen; Gemcitabine (1250 mg/m^2) day 1, 8 and Cisplatin (75mg/m^2) day 1 given intravenously with Metformin hydrochloride 500 mg oral tablets once daily as a 21-day cycle, for 6 cycles. Arm B (Control group): 15 patients received the Gemcitabine/ Cisplatin regimen alone. Gemcitabine (1250 mg/m^2) at day 1, 8 and Cisplatin (75mg/m^2) at day 1, were given intravenously as a 21-day cycle, for 6 cycles.

Procedures

At baseline, we recorded disease history, signs, and symptoms; did a physical examination, laboratory assessments, and computed tomography (CT) scans of the chest/abdomen and bone scan. Response to treatment was evaluated according to the version 1.1 of the response evaluation criteria in solid tumors guidelines (RECIST) basically after 3 cycles and after 6 cycles (if applicable). Toxicities were routinely categorized and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0). The protocol treatment was discontinued upon disease progression. All patients were routinely followed up by clinical assessment, laboratory testing and CT scans every 3 months for one year starting the first day of first cycle. Time to progression and time to death in months were recorded. Progression-free survival rates and one-year survival rates for both groups were calculated. All patients who died during the one-year follow up were considered progressed cases. The primary end point was to evaluate the ORR. The secondary end point was to evaluate PFS, OS, and the safety of the Metformin-Gemcitabine/

Table 1. Patients' Demographics and Baseline Characteristics

Parameter	Arm A	Arm B	p-value
Gender:			
Male: Number (%)	12 (80%)	13 (86.7%)	1.000[a]
Female: Number (%)	3 (20%)	2 (13.3%)	
Smoking History:			
Previous Smoker: Number (%)	11 (73.3%)	13 (86.7%)	0.651[a]
Never Smoker: Number (%)	4 (26.7%)	2 (13.3%)	
Age:			
More than or equal to 55 years: Number (%)	6 (40%)	10 (66.7%)	0.143[b]
Less than 55 years: Number (%)	9 (60%)	5 (33.3%)	
Age (years):			
Median (range)	56 (44-70)	52 (37-76)	0.062[c]
Number of metastatic sites: Exactly one:			
Number (%)	6 (40%)	7 (46.7%)	0.713[b]
More than one: Number (%)	9 (60%)	8 (53.3%)	
Bone metastasis: Number (%)	7 (46.7%)	8 (53.3%)	0.715[b]
Lung metastasis: Number (%)	6 (40%)	5 (33.3%)	0.705[b]
Malignant pleural effusion: Number (%)	4 (26.7%)	4 (26.7%)	1.000[a]
Brain metastasis: Number (%)	6 (40%)	2 (13.3%)	0.215[a]
ECOG PS:			
Score=1: Number (%)	14 (93.3%)	12 (80%)	0.598[a]
Score=2: Number (%)	1 (6.7%)	3 (20%)	
Hemoglobin level (g/dL): Median (range)	12.5 (10-15)	12 (10-14)	0.125[c]
Neutrophil count ($10^3/\mu$L): Median (range)	5.4 (2.7-7.4)	4.9 (2.9-7.6)	0.950[c]
Platelet count ($10^3/\mu$L): Median (range)	344 (197-464)	367 (287-544)	0.431[c]
Pathological subtype:			
Adenocarcinoma: Number (%)	9 (60%)	11 (73%)	---[d]
Squamous cell carcinoma: Number (%)	2 (13%)	2 (13%)	
Large cell carcinoma: Number (%)	4 (27%)	2 (13%)	

[a]Statistical test: Fisher's exact test, p-value > 0.05: non-significant; [b]Statistical test: Chi-squared (χ^2) test, p-value > 0.05: non-significant; [c]Statistical test: Mann-Whitney test, p-value > 0.05: non-significant; [d]The counts of patients were not enough to do a proper statistical test; Arm A: patients were treated with Gemcitabine/Cisplatin regimen in addition to daily 500 mg Metformin;
Arm B: patients were treated with Gemcitabine/Cisplatin regimen only; ECOG PS; Eastern Cooperative Oncology Group Performance Status

Cisplatin combination by estimation of treatment related toxicity.

The trial was conducted in accordance with the Declaration of Helsinki and good clinical practice guidelines. Ethical approval was obtained from the independent ethics committee before trial initiation. All participants provided written informed consent.

Statistical analyses

Data management and analysis were performed using Statistical Package for Social Sciences (SPSS) version 17. Non-parametric numerical data were summarized as medians and ranges. Categorical data were summarized as percentages. The Chi-squared test and Fischer's exact test were used to compare between the studied groups with respect to categorical data. Mann-Whitney test was used to compare between the studied groups with respect to non-parametric data. The Kaplan-Meier method was used to estimate the fraction surviving while Log rank test was used to compare survival data.

Results

From October 2011 to March 2013, a total of eighty stage IV NSCLC patients treated at the Clinical Oncology department, Ain Shams University were assessed for study eligibility and only thirty patients fulfilled the eligibility criteria and were enrolled in the study. Patients' demographics and baseline characteristics were balanced between the two arms of the study. Most of the patients enrolled in the study were male patients, ex-smokers with ECOG PS of 1. Adenocarcinoma was the dominant histological variant of NSCLC in the study population. The patients' characteristics data is represented in Table1.

The ORR to treatment in arm A was 46.7% compared to 13.3% in arm B, however this difference was not statistically significant with the p value=0.109. In the Metformin arm, six patients progressed two of them died and in the control arm, seven patients progressed three of them died. All patients enrolled in the study were followed for progression for a period of 1 year (12 months) starting day 1 of first cycle. Two patients (6.7%) survived for more than 1 year without progression. The overall median PFS for all patients enrolled was 5 months. The median PFS in arm A and arm B were 5.5 months and 5 months, respectively (p value=0.062). As demonstrated in Table 2, the effects of different potential prognostic factors on the PFS were studied. There was a statistically significant difference in PFS between those who developed NSCLC at an age more than 55 years and those at an age of 55 years or less (p value=0.040). Moreover, a statistically significant difference was observed between those who suffered from headache as an adverse event and those who did not (p value=0.006).

Twelve (40%) of patients enrolled in the study survived more than 12 months. The median survival time was 8 months. The median survival time for arm A and arm B were 12 months and 6.5 months, respectively. There was no statistically significant difference between the study arms in survival (p value=0.119). The Kaplan-Meier

Table 2. The Effect of Different Factors on Progression-free Survival

Factor		Total	Number of events	Percentage free of progression [a]	p-value [b]
Age at onset	more than 55 yr	14	12	28.60%	0.040*
	55 yr or less	16	16	18.80%	
Number of metastatic sites	One	13	12	15.40%	0.689
	More than one	17	16	29.40%	
Bone metastasis	No	15	13	33.30%	0.218
	Yes	15	15	13.30%	
Lung metastasis	No	19	18	21.10%	0.561
	Yes	11	10	27.30%	
Brain metastasis	No	22	21	18.20%	0.243
	Yes	8	7	37.50%	
Malignant Pleural Effusion	No	22	20	22.70%	0.851
	Yes	8	8	25.00%	
Smoking history	Never smoker	6	5	16.70%	0.792
	Ex-smoker	24	23	25.00%	
Anemia	No	19	17	26.30%	0.901
	Yes	11	11	18.20%	
Decreased platelets count	No	22	21	22.70%	0.397
	Yes	8	7	25.00%	
Decreased neutrophil count	No	22	20	31.80%	0.414
	Yes	8	8	0.00%	
Nausea	No	16	14	31.10%	0.567
	Yes	14	14	14.30%	
Vomiting	No	21	19	23.80%	0.592
	Yes	9	9	22.20%	
Pruritis	No	22	20	27.30%	0.714
	Yes	8	8	12.50%	
Headache	No	17	15	41.20%	0.006*
	Yes	13	13	0.00%	

[a]estimates of disease progression computed using Kaplan- Meier procedure; [b]Statistical test: Log rank test, p-value > 0.05: non-significant; *indicates statistical significance

Table 3. The Effect of Different Factors on Overall Survival

Factor		Total number	Number of events	Percentage surviving after 12 months [a]	p-value [b]
Age of onset	more than 55 yr	14	9	35.70%	0.119
	55 yr or less	16	9	43.80%	
Number of metastatic sites	One	13	5	61.50%	0.763
	More than one	17	13	23.50%	
Bone metastasis	No	15	7	53.30%	0.045*
	Yes	15	11	26.70%	
Lung metastasis	No	19	10	47.40%	0.101
	Yes	11	8	27.30%	
Brain metastasis	No	22	15	31.80%	0.277
	Yes	8	3	62.50%	
Malignant	No	22	12	45.50%	0.116
Pleural Effusion	Yes	8	6	25.00%	
Smoking history	Never smoker	6	3	50.00%	0.286
	Ex-smoker	24	15	37.50%	
Anemia	No	19	10	47.40%	0.444
	Yes	11	8	27.30%	
Decreased	No	22	13	40.90%	0.551
platelet count	Yes	8	5	37.50%	
Decreased	No	22	12	45.50%	0.832
neutrophil count	Yes	8	6	25.00%	
Nausea	No	16	9	43.80%	0.791
	Yes	14	9	12.80%	
Vomiting	No	21	12	42.90%	0.758
	Yes	9	6	33.30%	
Pruritis	No	22	14	36.40%	0.518
	Yes	8	4	50.00%	
Headache	No	17	8	52.90%	0.068
	Yes	13	10	23.10%	

[a]estimates of survival computed using Kaplan- Meier procedure; [b]Statistical test: Log rank test, p-value>0.05: non-significant; *indicates statistical significance

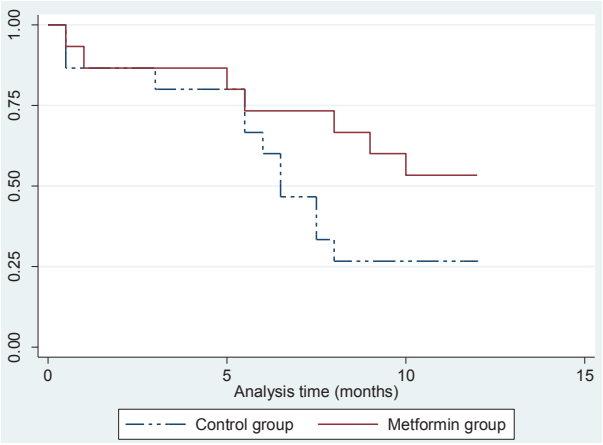

Figure 1. Kaplan-Meier Overall Survival Estimate in the Study Groups

estimates of OS in the study groups are represented by Figure 1. Table 3 shows the effects of different factors on the OS. There was a statistically significant difference in survival between those who had one metastatic site and those who had more than one metastatic site (p value=0.045).

Out of the thirty patients enrolled in the study, only one patient assigned to the Metformin group didn't report any adverse events and only one patient assigned to the control group suffered grade III adverse events (anemia). Metformin significantly reduced the frequency of patients who experienced nausea in the Metformin group vs. the control group (26.7% vs. 66.7%, respectively. p value=0.028) while there was no statistically significant difference in the occurrence of other adverse events between both arms.

Discussion

The current study showed that the addition of Metformin to Gemcitabine/Cisplatin protocol led to a clinically meaningful increase in the tumor ORR compared to Gemcitabine/Cisplatin protocol alone (46.7% vs. 13.3%, respectively). However, this increase was not found to be statistically significant, which might be attributed to the small sample size that weakened the power of the study. The heterogeneity of the NSCLC histological subtypes and genotypes among the patients enrolled in the study might have also contributed to the non-statistically significant results concerning tumor response. This point is also supported by the recent observation that Metformin and Cisplatin might be partly antagonistic in various histological subtypes of human lung cancer cell lines with the exception of adenocarcinoma (Janjetovic et al., 2011; Ashinuma et al., 2012). Moreover, it has been found that not only the histological stratification can differ, but also the genotype mutation encountered in the different types of NSCLC can as well affect the response. Recently, Ma and colleagues showed that Metformin induced apoptosis and inhibited cell proliferation in the Kras mutant tumors but not in the Kras wildtype tumor (Ma et al., 2013). Kras mutations showed a higher prevalence among patients

with lung adenocarcinoma (Forbes et al., 2006). The effect of Metformin on different histological subtypes and genotypes still needs further exploration.

In the current study, no statistically significant difference was observed between both groups regarding the PFS. The median time to progression in Metformin and control arms was 5.5 months and 5 months, respectively. The incremental gain in time to progression needed to predict a clinically meaningful survival would have been 2-3 months indicating that Metformin did not affect PFS (Maio et al., 2008). This study showed an increase in the median OS and one year survival rate in the Metformin group by 15% compared to the control group. However, this increase was not statistically significant probably due to the small sample size. This tendency to increase the OS is in accordance with the results of a retrospective cohort study by Tan and colleagues where diabetic NSCLC patients treated with Metformin demonstrated a better outcome in terms of OS compared with the outcomes produced with patients on insulin or other hypoglycemic drugs (Tan et al., 2011). Moreover, a meta-analysis by Ming et al, investigated the association between Metformin and OS in patients with cancer and type II diabetes. Twenty publications found that there was a relative survival benefit associated with Metformin treatment compared with treatment with other glucose-lowering medications in OS (hazard ratio: 0.66; 95% CI: 0.55-0.79) (Yin et al., 2013).

In the current study, the Metformin-dosing schedule used was well tolerated without any significant increase in the incidence of adverse effects which is consistent with other clinical studies showing that metformin long-term treatment was associated with few adverse effects in diabetic, as well as non-diabetic patient populations (Bolen et al., 2007; Tang et al., 2012). Metformin addition to chemotherapy led to a significant decrease in the occurrence of chemotherapy induced nausea, which could be attributed to the anti-inflammatory and anti-oxidant effects of Metformin (Chakraborty et al., 2011). Yet, the potential ability of Metformin to lower the toxicity associated with standard chemotherapy needs further evaluation.

An association between PFS and age of patients at diagnosis was observed in this study. Younger patients (55 years or less) showed a statistically significant lower PFS rate than older patients (more than 55 years). Similarly, a retrospective study evaluating the association between age at diagnosis and outcome in female patients with NSCLC, who were treated with Gefitinib, demonstrated that old age was a favorable factor in terms of PFS (Na et al., 2010). Moreover, a statistically significant association was observed between the development of headache and the decrease in PFS. This association can be explained by the fact that 4 of the 13 patients who reported headache as an adverse event suffered from brain metastasis and 3 of these patients developed brain metastasis upon disease progression. Similarly, Ceresoli and colleagues have previously demonstrated that the prognosis of NSCLC patients with brain metastases was poor with a median PFS of 3 months (Ceresoli et al., 2004). The presence of four cases of early death before disease progression among the patients who developed headache during the study might have contributed to the lower PFS in this group of patients. This study also showed a significant association between OS and the number of metastatic sites (exactly one site or more than one). Patients with exactly one site of metastasis showed higher overall one-year survival rate (61.5%) compared to those with more than one metastatic site (23.5%). This is in agreement with the results of several studies that showed that a single site of distant metastasis was considered a significant favorable factor in long-term survival (Paesmans et al., 1995; Okamoto et al., 2005).

Finally, Metformin at a dose of 500 mg per oral once daily for patients treated with Gemcitabine/Cisplatin regimen led to significant decline in the occurrence of chemotherapy-induced nausea and was well tolerated. The Metformin group showed a clinically relevant increase in both OS and response rates, yet these results did not attain statistical significance. According to the potentially favorable results observed in the current study, we recommend the conduction of larger, multicenter, randomized clinical trials on Metformin to confirm these results and to emphasis Metformin's role on the different histological subtypes of NSCLC.

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