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Circulating Tumor Cells Failed to Predict Prognosis Following Micro-Wave Ablation of Oligometastasis in EGFR-mutant Non-Small Cell Lung Cancer Patients

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Abstract

Microwave ablation (MWA) in conjunction with EGFR inhibition has been shown to be effective for treating EGFRmutant non-small cell lung cancer patients with oligoprogressive disease. However, patients who will benefit most from MWA is inconclusive. The circulating tumor cell (CTC) count during EGFR-targeting tyrosine kinase inhibitors has been used to predict survival outcomes. This study aimed to explore the prognostic significance of the baseline CTC count and the change in the CTC count during MWA therapy of patients with EGFR-mutant NSCLC.

Serial blood samples were taken at baseline (CTC-d0) and on day 28 (CTC-d28) following MWA for detection of CTCs. 36 patients were eligible and thirty-five of these patients had CTC-d0 \geq 2. Patients were dichotomized as favourable (0-8 CTCs) and unfavourable (\geq 8 CTCs) groups according to CTC numbers. The progression-free survival (PFS) interval for patients in the favourable group at baseline was 8.5 months, similar with the median PFS time of 8.1 months achieved by patients in the unfavourable group (p=0.231). In addition, patients in the favourable group on day 28 did not exhibit significantly longer median PFS compared with patients in the unfavourable group (8.3 vs. 7.9 months; p=0.147). The overall survival outcome is not mature. In univariate analysis and multivariate analysis, CTC-d0 \geq 8 vs. CTC-d0<8 and CTC-d28 \geq 8 vs. CTC-d28 <8 were not significantly associated with poor PFS. This study indicates that the CTC count is not a prognostic factor for PFS outcome following MWA in patients with EGFR-mutant NSCLC.

Keywords: Microwave ablation; Circulating tumor cell; Non-small cell lung cancer

Introduction

Lung cancer is one of the most prevalent cancers and the leading cause of malignant tumor related death in China and worldwide [1]. Epithelial growth factor receptor (EGFR) mutations are present in approximately 10% of White non-small cell lung cancer (NSCLC) patients and in 30% of Asian NSCLC patients [2,3]. EGFR-targeting tyrosine kinase inhibitors (TKIs) have been established as first-line treatment for positive EGFR-mutant NSCLC patients [4-7]. Despite the initial response is favourable, the vast majority of patients will have disease progression and acquire resistance to these EGFR-TKIs [8].

Recently, a series of studies showed local therapy including radiation, microwave ablation (MWA) and radio-frequency ablation (RFA) with continued EGFR inhibition was effective in treating EGFRmutant patients with oligoprogressive disease such as intracranial disease progression, development of fewer than 5 discrete sites of disease while the patient remains asymptomatic [9-11]. However, there is no consensus or any predicator showing who will benefit most from local therapy.

Circulating tumor cells (CTCs) have recently emerged as important potential biomarkers of diagnosis, evaluation of treatment effect, and prognosis in several epithelial cancers [12-14]. In NSCLC, CTCs have been detected in blood at different time points throughout disease treatment and changes in CTC numbers have demonstrated the prognostic significance [15].

In this study, we aimed to explore the clinical significance of the baseline CTC count and the change in the CTC count during MWA therapy with continued EGFR-TKIs to predict survival outcomes in patients with EGFR acquired resistance NSCLC with non-central nervous system (CNS) oligoprogressive disease.

Methods

Eligible patients had to have EGFR-mutant lung cancer previously treated with first-line Erlotinib or Gefitinib, have documented oligoprogression on first-line therapy, and then undergone MWA of the oligoprogressive disease. All patients underwent CNS imaging and bone scintigraphy prior to MWA and avoiding the treatment in the setting of bone or brain metastasis. All patients continued the same TKIs following MWA treatment. The whole procedures of MWA were performed under CT guidance and the detailed procedures were described in previous publication [16]. All patients provided written informed consent; the study was approved by the ethics committee of Weifang People's Hospital and conducted according to the Declaration of Helsinki principles.

All patients underwent a baseline blood draw before MWA for assessment of CTCs using the Cyttel method provided by Cyttel

Biosciences Co., Ltd., (Beijing, China). The fundamental principles of this method comprise two components: one is for CTCs enrichment that is based on negative enrichment by immunomagnetic beads, and the other is for CTCs detection and quantification that is based on CD45 immunostaining and fluorescence in situ hybridization (FISH) using anti-human CD45 and probes against the centromere of chromosome 8 respectively, the detailed procedures were described in previous publication [17].

Statistical analysis

Patients were divided into the favourable group (CTC<8/sample) and the unfavourable group (CTC \geq 8/sample) as defined before [17]. Baseline (CTC-d0), day 28 following MWA (CTC-d28), performance status (PS) , and tumor stage were subjected to univariate Cox proportional hazards regression analysis for progression-free survival (PFS). Univariately significant parameters were then included in a multivariate Cox proportional hazards regression analysis. PFS was measured from the date of MWA to the date of radiological progression according to Revised Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 or was censored at the last follow-up. Statistical analyses were performed using the GraphPad Prism (GraphPad Software, San Diego, CA, USA) and SPSS version 18.0 software (SPSS, Inc., Chicago, IL, USA), where a value of p<0.05 was considered to be statistically significant.

Results

Prevalence of CTC at baseline

From December 2015 to November 2016, 36 consecutive patients signed informed consent and were enrolled in the study. All patients with oligoprogressive disease received MWA followed by continuation of the same EGFR-TKIs. Thirty-eight metastatic sites of lung, adrenal and lymph node were ablated. Most MWAs were well tolerated during the procedure and no patients died within 30 days after MWA. The common side effects including pain, fever, pneumothorax, pleural effusion and haemoptysis occurred in12 patients (34.2%),10 patients (28.6%), 5 patients (14.2%), 2 patients (5.7%), and 3 patients (8.6%) respectively.

At the time of analysis, all of the patients had experienced disease progression. Thirty-five patients had CTC-d0 of ≥ 2 at baseline (before MWA treatment), among the patients that were positive for ≥ 2 CTCs per sample, 15 patients had CTC-d0 <8 and 20 patients had CTC-d0 ≥ 8 , respectively. The prevalence of CTCs and clinical characteristics of these patients before MWA treatment are noted in Table 1. A CTC-d28 analysis was not available in 1 patient because of blood sample processing errors. Of the 15 patients with a CTC-d0 of 2–8, 12 had a CTC-d28 of 0–8, whereas 3 had a CTC-d28 of ≥ 8 ; Of the 20 patients with a CTC-d0 of ≥ 8 , 12 had a CTC-d28 of 0–8, whereas 7 had a CTC-d28 of ≥ 8 .

Characteristics	Total (n=35)	CTCs at baseline						
		2-8 (n=20)	≥ 8 (n=15)					
Gender, n (%)								
Male	21 (60%)	11 (55%)	10 (45%)					
Female	14 (40%)	9 (65%)	5 (35%)					

Age, n (%)							
≥ 60	20 (59%)	12 (60%)	8 (40%)				
<60	15 (41%)	8 (53%)	7 (47%)				
Tumor stage, n (%)							
IIIB	27 (77%)	17 (62%)	10 (38%)				
IV	8 (23%)	3 (38%)	5 (62%)				
Baseline WHO PS, n (%)							
PS=0-1	23 (62%)	15 (65%)	8 (35%)				
PS=2	12 (38%)	5 (41%)	7 (59%)				
Treatment received, n (%)							
Erlotinib	19 (54%)	10 (51%)	9 (49%)				
Gefitinib	18 (46%)	10 (52%)	8 (48%)				
Smoking status, n (%)							
Ever smoker	22 (65%)	13 (59%)	9 (41%)				
Never-smoker	13 (35%)	7 (52%)	6 (48%)				
No. of affected organs, n (%)							
0-1	25 (71%)	16 (63%)	9 (37%)				
>1	10 (29%)	4 (40%)	6 (60%)				
Abbreviations: PS, performance status; CTC, circulating tumor cell.							

 Table 1: Prevalence of CTCs before micro-wave ablation.





Prognostic value of the CTC

Patients were divided into favourable (CTC-d0 of<8, n=15) and unfavourable (CTC-d0 of ≥ 8 , n=20) prognostic groups. The median PFS time in the favourable group was 8.5 months, failed to show a survival advantage when compared with the unfavourable group: 8.1 months (p=0.231) (Figure 1), but significantly longer than the three patients who demonstrated an increase in CTC number after MWA, with PFS durations of 7.6 months (p=0.049). In addition, 24 patients with a CTC-d28 of<8, and 10 patients with a CTC-d28 of ≥ 8 , the

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median PFS interval in the favourable group was similar with the unfavourable group: 8.3 months *vs.* 7.9 months (p=0.147) (Figure 2).



Figure 2: Progression-free survival outcome according to CTC count on day 28.

Univariate and multivariate analyses

In the univariate analysis, CTC-d0 $\geq 8 vs.$ CTC-d0 <8 was not a significant prognostic factor for poor PFS, the p-value was 0.539 [hazard ratio (HR): 1.755, 95% CI: 0.667–2.859]; CTC-d28 $\geq 8 vs.$ CTC-d0 <8 was also not a significant prognostic factor for poor PFS with p-value=0.917 [hazard ratio (HR): 2.579, 95% CI: 0.721–3.537] (Table 2).

Discussion

Local therapy had been shown to be effective for treating NSCLC with oligoprogressive disease and associated with better survival outcomes. Ni and his colleagues reported that patients with non-CNS oligoprogressive disease had a longer PFS interval after MWA when compared with a transformation to platinum-based chemotherapy [11]. In addition, Wei et al. showed that advanced NSCLC could have a better PFS interval from a combination of MWA at primary tumor sites and platinum-based doublet chemotherapy when compared with chemotherapy alone [18].

Covariates	Univariate analysis			Multivariate analysis					
	HR	95% CI	P value	HR	95% CI	P value			
CTC-d0 (≥ 8 <i>vs</i> . <8)	1.755	0.667–2.859	0.539	-	_	_			
CTC-d28 (≥ 8 <i>vs</i> . <8)	2.579	0.721–3.537	0.917	-	_	_			
PS (2 vs. 0–1)	4.107	2.917–7.041	0.007	5.131	2.707–8.795	0.033			
Tumor stage (IV vs. IIIB)	2.136	1.011–6.371	0.015	3.051	1.173–7.201	0.023			
Abbreviations: CI, confidence interval; HR, hazard ratio; CTC, circulating tumor cell.									

Table 2: Univariate and multivariate analysis for progression-free survival outcomes.

In 2013, a study conducted by Yu et al. [10] enrolled eighteen EGFRmutant non-small cell lung cancer patients with acquired resistance to EGFR-TKI therapy. In conjunction with continued EGFR inhibition, all the patients underwent local therapy including radiation therapy, radiofrequency ablation, or surgical treatment of a site of progressive disease. The study showed that survival outcomes after local therapy appeared to be best for those who had the known site of metastasis. In addition to analysis of clinical characteristics, site of metastasis and rate of tumor growth, molecular biomarkers such as CTCs or ctDNA may be helpful to identify the candidates most likely to have good outcomes after local therapy.

The baseline CTC count and the change in the CTC count during treatment had been used to predict survival outcomes for NSCLC. In 2012, Krebs et al. used the cell search technology to emanate CTCs from 101 stage III-IV NSCLC patients, a cut-off value of >5 correlated with shorter PFS and OS, in addition, decrease of CTC numbers with one cycle of standard chemotherapy corresponded to improved PFS and OS [15]. Additionally, a meta-analysis performed by Wang et al. showed that the presence of CTCs was associated with a poorer outcome than a lack of CTCs, and CTCs were strongly associated with reduced survival [19]. Targeted therapies have become a main-stay option for NSCLC patients with mutations. Recently, He et al. reported the CTC measurement could be used to predict the efficacy of first-line EGFR-TKI treatment and prognosis of advanced NSCLC [20].

Moreover, Yang et al. showed the CTC measurement could be used to predict the efficacy of second-line treatment using AZD9291 following first-line EGFR-TKIs of advanced NSCLC [21]. However, data on the relationship between CTCs and local therapy including MWA for NSCLC was lacking, we first analysed the baseline CTC and the change in the CTC count after MWA for patients with EGFR acquired resistance NSCLC with non-CNS oligoprogressive disease, and showed that neither CTC-d0 before MWA nor CTC-d28 following MWA were prognostic biomarkers in these patients.

It should be noted that the number of patients with samples at both time points was relatively small, and the small sample size may have introduced bias in the results. Recently, there has been a move from CTC counts to molecular and genetic analysis of CTCs and the use of CTCs as potential real-time liquid biopsies to facilitate personalized medicine. Additionally, sequencing-based evaluation of CTCs or cfDNA analysis may ultimately become a more clinically meaningful tool than merely isolation of CTCs.

In summary, this is the first report over the presence of CTCs and its prognostic role during MWA therapy with continued EGFR-TKIs in patients with EGFR acquired resistance NSCLC. The use of serial CTC evaluation as a surrogate biomarker should not be recommended for individuals to be received MWA. Citation: Zheng D, Ren H, Liu S, Li R, Zhang Q, et al. (2018) Circulating Tumor Cells Failed to Predict Prognosis Following Micro-Wave Ablation of Oligometastasis in EGFR-mutant Non-Small Cell Lung Cancer Patients. J Carcinog Mutagen 9: 321. doi: 10.4172/2157-2158.1000321

Conflict of Interest

There is no conflict of interest.

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