Cancer Treatment and Research Communications 19 (2019) 100126

Contents lists available at ScienceDirect

Cancer Treatment and Research Communications

journal homepage: www.elsevier.com/locate/ctarc

Phase II study of stereotactic radiosurgery for the treatment of patients with oligoprogression on erlotinib

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ARTICLE INFO

Keywords:
Stereotactic radiosurgery
Oligoprogression
EGFR
Erlotinib

ABSTRACT

Introduction: Retrospective studies have evaluated the approach of stereotactic radiotherapy (SRT) to address oligoprogression in patients with *EGFR* mutant NSCLC on TKI therapy, it has never been prospectively studied.
Materials and methods: We treated 25 patients with *EGFR* mutant NSCLC on erlotinib who had 3 or fewer sites of extra-cranial progression with SRT to progressing sites, followed by re-initiation of erlotinib.
Results: Median PFS from the initiation of SRT was 6 months (95% CI 2.5 to 11.6) and median OS was 29 months (95% CI 21.7 to 36.3). Neither baseline nor changes in the Veristrat proteomic predicted PFS.
Conclusions: SRT and TKI continuation may be considered for select patients with *EGFR* mutant NSCLC and oligo-progression on EGFR TKI therapy.

Introduction

EGFR mutations are present in about 15% of patients with stage IV adenocarcinoma of the lung. Randomized studies comparing EGFR tyrosine kinase inhibitors (TKIs) to platinum-based doublet chemotherapy have consistently shown superior progression free survival (PFS) with TKIs, but median PFS is limited, at a median of 10 months with 1st generation agents [1] and 19 months with third generation agents [2]. At the time that this study was designed, second line therapy in this population was typically chemotherapy, with a much more challenging adverse event profile compared to targeted therapy.

At the time of progression, results can be heterogenous, with some locations of disease well controlled on TKI therapy while others progressing. Multiple data points converged to suggest the potential merits of using stereotactic radiotherapy (SRT) to prolong benefit from TKIs in patients with such oligo-progression. Biologically, *EGFR*-mutated NSCLC is more sensitive to radiation, both in vitro [3,4] and in-vivo [5]. Several phase II studies have shown favorable results in the oligo-*metastatic* state [6–9]. Finally, several retrospective series showed favorable results with locally ablative therapy to oligoprogression in driver oncogene-positive NSCLC [10,11]. We sought to prospectively evaluate the approach.

We also sought to evaluate and characterize the role of the serum proteomic signature Veristrat in patients with oligoprogression on erlotinib. Veristrat is a serum-based proteomic assay performed using matrix-assisted laser desorption/ionization (MALDI) mass spectrometry. Veristrat is both prognostic and predictive of differential benefit from erlotinib in the second-line treatment of unselected patients [12]. We hypothesized that if Veristrat reflected a systemic milieu favorable to EGFR TKI treatment, subjects would enter the study with an unfavorable signature ("poor") as a result of ongoing progression, and that the favorable/unfavorable status might be influenced by ablative therapy to the areas of progression.

Materials and methods

Subjects had stage IV *EGFR* mutant NSCLC with a previous response to EGFR-TKI or at least six months without progressive disease. ECOG PS of 0 or 1 was required. Standard end-organ functions were required. Prior radiation to sites of progression was not allowed. Up to five sites of intra or extra-cranial progressive disease on an EGFR TKI were allowed. The protocol provided detailed site-specific guidance regarding

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https://doi.org/10.1016/j.ctarc.2019.100126

stereotactic radiation regimen. These and other details can be found in the full protocol. Following stereotactic radiation, erlotinib was given per standard of care guidelines.

The primary statistical objective was to estimate PFS. We hypothesized that median PFS from the time of ablative therapy would be at least three months. This was conceptually based on a then current bar of minimal PFS efficacy established by the FDA approvals of erlotinib, pemetrexed and docetaxel in the 2nd line. We noted that a sample size of 40 patients would allow us to detect 70%, or 28/40 patients free of progression at 3 months with a 95% confidence interval of 53%−83%.

The study was approved by the Lineberger Comprehensive Cancer Center Protocol Review Committee and the University of North Carolina Institutional Review Board, as well as relevant regulatory committees at collaborating sites. It was conducted in accordance with the Declaration of Helsinki. The study was registered at clinicaltrials.gov (NCT01573702).

Results

25 patients were accrued between 12/2012 and 06/2016. The study closed early due to poor accrual and the development of second line therapy with osimertinib. Demographics are shown in Table 1. Of note, all subjects were being treated with the 1st generation *EGFR* TKI erlotinib at the time of study entry. Metastatic sites present included bone (55%), brain (40%), lymph nodes (40%), and liver (30%) (Figs. 1 and 2). The median PFS from the initiation of SRT was 6 months, and the median duration of erlotinib post SRS was 5.7 months (interquartile range 2–11 months). 16 subjects (64%) had PFS > 3 months. 3 subjects had PFS longer than 1 year; all were treated to a single lung lesion. 2 subjects are without progression and on erlotinib at followup times of 1.8 years and 2.8 years. A third subject progressed at 2.2 years.

While up to five sites were allowed, no patient was treated to more than 3 sites—21 were treated to one site, 2 to 2 sites and 1 to 3 sites. Treated lesions included bone (7), brain (2), liver (4), lung (15). No toxicity above grade 2 was attributed to SRS. Toxicities occurring in at least two patients from SRS were: fatigue (4 grade 1), pain (2 grade 1, 1 grade 2), and anorexia (2 grade 1). Toxicities occurring in at least two patient or grade 3 or higher and attributed to erlotinib re-treatment are shown in Table 2.

All subjects had a Veristrat "good" proteomic signature at baseline. The single "poor" signature changed to "good" following SRS, so all subjects had "good" signatures post SRS. No signature subsequently changed to "poor" at progression.

Table 1
Demographics.

Age	Median 64	Range 44–82
Race		
White	25	100%
Gender		
Female	16	64%
Male	9	36%
Smoking Status		
Never	16	69.6%
Former	7	30.4%
ECOG PS		
Fully active (0)	16	64%
Restricted (1)	9	36%
Mutation type		
Exon 19	14	56%
Exon 21	7	28%
Exon 19+ ALK rearrangement	1	4%
Exon 18 and Exon 20	1	4%
None proven; met clinical criteria	2	8%
CCMI	Median 6	Range 0–10

AbbreviationsL CCMI: Charlson Co-morbidity Index.

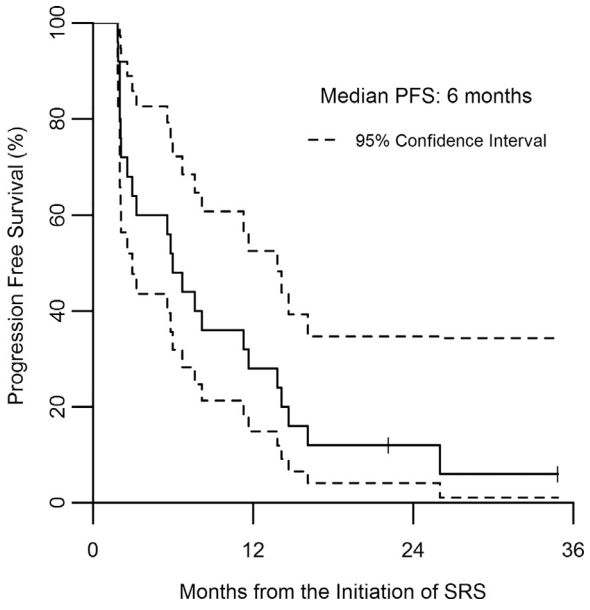

Fig. 1. PFS.

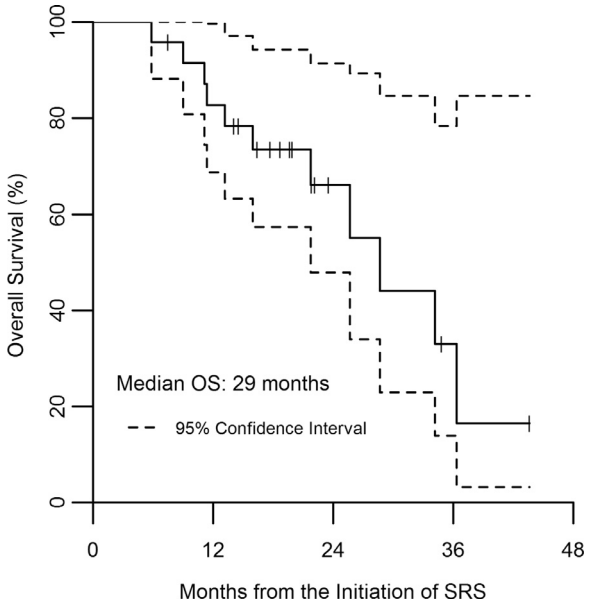

Fig. 2. OS.

Table 2
Toxicities attributed to erlotinib.

	Grade 1	Grade 2	Grade 3
Acneiform rash	5	2	2
Diarrhea	2	1	0
Fatigue	2	1	0
AST increased	2	0	0
Nausea	2	0	0
Paronychia	2	0	0
Weight loss	2	0	0

Discussion and conclusions

This study closed early due to poor accrual, which was likely impacted by the development of newer therapies for patients with EGFR-mutated NSCLC. Oligo-progression represents only a portion of EGFR progression events. During the conduct of the study, third generation

EGFR TKIs became available on clinical trials for patients with *T790M* resistance mutation, which represents 60% of cases of acquired resistance to first generation TKIs. Although the study was never powered to allow formal testing of a specific hypothesis, the limited accrual results in a 95% confidence interval wider than intended. We hypothesized that median PFS would be greater than 3 months in 70% (28) of treated patients, which would have provided a 95% confidence interval of 53%−84%. We observed 16/25 or 64% progression free at 3 months, which gives a 95% CI of 42.5% to 82.0%.

The median PFS of 6 months is consistent with outcomes seen in retrospective series, suggesting that some patients can be continued past progression on EGFR TKIs. To our knowledge, we are the first to report a prospective study of the approach of SRT followed by re-initiation of TKI for patients with oligo-progression. This data, along with 2 retrospective studies supports guidelines [13] that endorse the approach for select patients. Of course, neither this study nor retrospective reports prove clinical benefit from the SRT. It remains possible that some of these patients could have achieved similar results with continuation of erlotinib post progression and without SRT intervention. Despite this limitation, the use of SRT to address oligo-progression has been expanded in clinical practice to also be considered also in the context of 3rd generation EGFR TKI treatment, with TKIs in other driver oncogene-addicted tumors, and with immunotherapy. Critically, toxicity of stereotactic radiotherapy were limited, as was toxicity of subsequent re-initiation of TKI. Although the treatment of oligo-metastatic disease has been evaluated in a randomized study in patients with advanced NSCLC without regard to molecular subtype [6], such study remains an unmet need in oligo-progressive disease.

All but one subject entered the study with a “good” proteomic signature, suggesting that oligoprogressing patients may have a more favorable prognosis that those with more generalized progression. This is also supported by the median OS of 29 months. Although we had further hypothesized that at progression, “good” signatures would turn to “poor” this did not occur. Thus, Veristrat serum proteomics does not have a role in determining which patients with oligoprogression on erlotinib will benefit most from an SRT approach and should not be used as an early marker of progression.

Funding

This work was funded by Astellas.

Clinical practice points

Stereotactic radiosurgery is frequently considered in clinical practice in response to oligoprogression in patients being treated with targeted therapy. Prospective data now supports prior retrospective work supporting this practice.

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