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Stereotactic Radiotherapy Can Safely and Durably Control Sites of Extra-CNS Oligoprogressive Disease in ALK-Positive Lung Cancer Patients on Crizotinib

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Abstract

Purpose—A preliminary analysis demonstrated that local ablative therapy (LAT) can provide short-term control of extra-CNS (eCNS) lesion progression in tyrosine-kinase addicted non-small cell lung cancer (NSCLC) patients. However, little is known about the long-term efficacy and safety of single and multiple courses of radiotherapy when used to treat these sites of progressive disease. This study analyzes the durability and toxicity of radiotherapeutic LAT applied to eCNS disease progression in ALK+ NSCLC patients.

Materials and Methods—ALK+ NSCLC patients receiving crizotinib manifesting 4 discrete sites of eCNS progression were classified as having oligoprogressive disease (OPD). If subsequent progression met OPD criteria, additional courses of LAT were considered. Crizotinib was continued until eCNS progression was beyond OPD criteria or otherwise not suitable for further LAT.

Results—33 of 38 patients progressed on crizotinib. Of these, 14 had eCNS progression meeting OPD criteria suitable for radiotherapeutic LAT. Patients with eCNS OPD received 1–3 courses of LAT with radiotherapy. The 6 and 12 month actuarial local lesion control rates (LC) with radiotherapy was 100 and 86%, respectively. The 12 month LC with single-fraction equivalent dose >25 Gy versus ≤25 Gy was 100% vs. 60% ($p = 0.01$). No acute or late grade >2 radiotherapy-related toxicities were observed. Median overall time on crizotinib among those treated with LAT versus those who progressed but were not suitable for LAT was 28 and 10.1 months, respectively. Patients remaining on crizotinib for >12 months vs ≤12 months had a 2 year OS of 72% vs 12%, respectively ($p < 0.0001$).

Conclusions—LAT safely and durably eradicated sites of individual lesion progression in ALK+ NSCLC patients receiving crizotinib. A dose-response relationship for LC was observed. The

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suppression of OPD on crizotinib by LAT allowed an extended duration of exposure to crizotinib, which was associated with longer OS.

INTRODUCTION

Crizotinib (Pfizer, New York, NY) is a tyrosine kinase inhibitor (TKI) associated with a high response rate and prolonged progression-free survival (PFS) in metastatic anaplastic lymphoma kinase positive (ALK+) NSCLC [1–3]. Eventually, patients develop acquired resistance through a diverse array of mechanisms with a median PFS of 8–10 months [4–7].

While progression would traditionally direct a change in systemic therapy, within the initial crizotinib studies patients were allowed to remain on the drug post-progression if, in the opinion of the investigator, there was evidence of ongoing clinical benefit [8]. We previously published a preliminary analysis of our institutional experience of metastatic EGFR mutation positive or ALK+ NSCLC patients who developed central nervous system (CNS) or extra-CNS (eCNS) oligoprogressive disease (OPD) while on erlotinib or crizotinib, respectively, who then received local ablative therapy (LAT), either surgery or radiation [9]. OPD here is defined as 4 or fewer discrete lesions amenable to invasive or non-invasive ablation. In this mixed population, the use of LAT and ongoing TKI therapy was associated with 7.1 and 4 months of additional disease control after CNS and eCNS progression, respectively. However, the safety and efficacy of multiple different courses of LAT for eCNS OPD have not been previously described.

Here, we report a mature analysis of the ALK+ cohort with over 2 years of clinical and imaging follow-up to more fully explore the use of LAT in controlling the emergence of eCNS resistance allowing maximal continued benefit from crizotinib.

MATERIALS AND METHODS

Patients

Thirty eight ALK+ NSCLC patients treated with crizotinib either on or off an IRB approved study between March 2009 and August 2013 were identified (Table 1). No patients were excluded in this analysis. ALK status was determined as previously described [3]. PFS was defined as the interval between start of treatment and disease progression on imaging per RECIST 1.1, or clinical progression as determined by the treating physician. Patients received systemic imaging at 6–8 week intervals. Overall PFS included both CNS and eCNS progression events. Time interval to initial eCNS progression was defined as PFS1, and subsequent eCNS progression (PFS2, PFS3, etc) was defined as the interval between the prior time of progression and the next imaging study demonstrating further progression. Data from these patients were captured and analyzed in accordance with an IRB approved institutional protocol covering clinical information relating to molecularly profiled thoracic oncology patients at the University of Colorado.

Local Ablative Therapy

Patients with eCNS OPD (4 or fewer discrete progressing lesions) were evaluated by a multidisciplinary lung team at tumor board. Those who continued to derive systemic benefit

from crizotinib, were ECOG 0–1 and had lesions amenable to invasive or non-invasive ablation were considered appropriate for LAT, which consisted of either hypofractionated radiotherapy (HRT), stereotactic body radiation therapy (SBRT) or surgery to the sites of OPD. Patients who developed CNS progression received fractionated radiotherapy or radiosurgery to these lesions, but CNS progression was considered an independent event with respect to eCNS progression.

All patients eligible for LAT radiotherapy underwent CT-based simulation with construction of customized body molds for treatment immobilization. Patients with pulmonary or liver lesions underwent 4D-CT simulation with abdominal compression in order to account for breathing-related tumor motion. For all other lesions where breathing-related motion was considered negligible, gross tumor volume was contoured from conventional CT simulation images. SBRT was planned and delivered using dynamic conformal arcs or multiple coplanar static beams according to methods previously described [10, 11]. Patients withheld crizotinib only on the days they were to receive LAT and continued on all other days. HRT was used when nearby normal tissue dose constraints would be exceeded if the radiotherapy was given in 5 or fewer fractions.

To compare the biological impact of different dose fractionation schemes on local control rates, we used total dose and also the single fraction equivalent dose (SFED) index described by Park et al [12]:

$$\begin{aligned} \text{For } d < D_T: \quad SFED &= \alpha D_0 D \left(1 + \frac{d}{\beta} \right) \\ \text{For } d \geq D_T: \quad SFED &= D - (n-1) D_q \end{aligned}$$

where D_T is the transition dose between the linear quadratic model and multi-target model, d is the dose per fraction, D is the total dose, D_0 is the dose required to reduce the surviving fraction of cells to 37%, and n is the total number of fractions. The assumed values for D_T , D_0 , α/β and α are 6.1 Gy, 1.25 Gy, 8.6 Gy, and 0.33 Gy^{-1} , respectively.

Patients treated with LAT were followed for subsequent disease progression. Acute and late toxicity was evaluated using the NCI Common Toxicity Criteria for Adverse Events (CTCAE) v4.0 during and up to 3 months following LAT. Late toxicity was scored as occurring 3 months after completion of LAT. Fourteen patients had over 3 months of toxicity follow-up and 12 (86%) had over 12 months of toxicity follow-up.

End Points and Statistical Analysis

Kaplan Meier (KM) analysis was calculated to determine actuarial local control rates (LC) and overall survival (OS). OS and PFS rates between patients treated with LAT vs no LAT; the effect of dose and SFED on LC; and length of time on crizotinib were performed using log-rank analysis with a p value ≤ 0.05 considered statistically significant (GraphPad Prism®, La Jolla, CA). OS was calculated from the date of first crizotinib dose to last follow-up or time of death.

RESULTS

Patient Characteristics

The median follow-up for all patients was 25.1 months. At the time of analysis, 33 patients had experienced first progression, either in the CNS (n = 13), eCNS (n = 18), or both (n = 2) (Figure 1). Overall, 14 patients with eCNS OPD received LAT at initial eCNS progression, 13 of whom received radiotherapeutic LAT alone and one who received surgery (adrenalectomy) followed by an additional course of radiotherapeutic LAT. The median overall PFS1 in the 38 ALK+ patients was 9.1 months (range: 1.1 –41.1). Median eCNS PFS1 was 17 months (range: 1.1 – 34).

A total of 29 eCNS OPD lesions treated with radiotherapy were identified (1st course of LAT: 19 lesions, 2nd: 7 lesions, and 3rd: 3 lesions). Sixteen were treated using SBRT (12 – 54 Gy/1–3 fractions) and 13 were treated using HRT (30 – 40 Gy/10 fractions). LAT was completed at a median of 36.5 days from the time of radiographic lesion detection (range 8 – 154). The upper end of the range reflects 3 patients who completed their course of SBRT 102, 107 and 154 days after the reported progressing lesion was first detected, due to back dating suspicious lesions detected by CT that were only confirmed (by PET/CT) at a later date.

Radiotherapy Toxicity

Eight patients (57%) treated with LAT reported symptoms attributable to radiotherapy. Acute grade 1 toxicities included fatigue (n = 4), chest wall/rib discomfort (n = 3), abdominal discomfort (n = 3), nausea (n = 3), diarrhea (n = 2), and anorexia (n = 2). The only grade 2 toxicity was fatigue (n = 1). Late grade 1 toxicities included fatigue (n = 2), chest wall pain (n = 3), nausea (n = 1), diarrhea (n = 2), anorexia (n = 2), truncal/arm edema (n = 1) and rash (n = 1). Late grade 2 toxicities included fatigue (n = 1), abdominal pain (n = 1) and radiation pneumonitis (n = 1), and shoulder/arm pain (n = 2). No acute or late grade 3–5 toxicities were observed.

Local Control

The median imaging follow-up for all 14 LAT-treated patients was 11.5 month (range: 2 – 39). Actuarial 6 and 12 month LC were 100% and 86%, respectively (Figure 2a). Lesions receiving HRT (n = 14) had a 6 and 12 month local control rate of 89% (1 failure) and 58% (3 cumulative failures), respectively, while lesions treated with an SBRT regimen (n = 15) had both a 6 and 12 month local control rate of 100%. The 3 lesions that experienced local failure all occurred within a single patient who received HRT and experienced in-field radiotherapy failure with a median local progression time of 6 months (range: 6 – 8). Due to proximity to this patient's brachial plexus, all three treated lesions received 35 Gy/10 fractions. When lesion control and time to failure were stratified by overall total dose (Figure 2b) or by SFED (Figure 2c), we observe that higher total doses (>40 Gy, p = 0.12) and higher SFED (>25 Gy, p = 0.01) were associated with improved local lesion control.

Additional LAT and Duration of Clinical Benefit from Crizotinib

The median duration of crizotinib exposure in the 38 ALK+ patients was 17 months (1 – 44). The median PFS1 for the 14 ALK+ patients who received LAT (including the one treated with surgical LAT) was 14 months (range 5 – 25). In a group of 13 patients with eCNS only progression not eligible for LAT (widespread systemic disease, poor KPS, or OPD and switched to alternative systemic therapy), PFS1 was 7.2 months (range 1.1 – 28.2). The median eCNS PFS2 in the LAT cohort was 5.5 months (range: 1–27). PFS2 was longer at 7 months (range: 3 – 27) vs 2 months (range: 1.1 – 6) in patients who received LAT for 1 – 2 vs 3 – 4 lesions of eCNS OPD at PFS1, respectively, but the difference was not statistically significant ($p = 0.12$). We evaluated whether patients with 1–2 lesion vs 3–4 lesions at PFS1 had a difference in time to first progression (PFS1). Median duration of crizotinib exposure in the LAT cohort (including 1st, 2nd and 3rd courses in addition to continued maintenance crizotinib if demonstrating ongoing clinical benefit) was 28 months (range: 7.7 – 43.8) (Figure 3). Figure 4 shows how, in a single patient, serial PET/CT scans were used to track response and progression on crizotinib and the effectiveness of multiple courses of LAT.

At the time of analysis, 20 (53%) of the 38 patients had died. The median, 1-year and 2-year OS were 39 months, 86%, and 57%, respectively (Figure 5a). Patients who remained on crizotinib for >12 months had a significantly improved OS at 2 years compared to those patients who had ≤12 months of crizotinib treatment (72% vs 12%, $p = 0.0001$) by log-rank analysis (Figure 5b).

DISCUSSION

Aggressive local therapy for patients with oligometastatic disease (e.g. resection of isolated hepatic metastases from colorectal cancer), has shown improved OS compared to historical controls [13–15]. Here we describe using a similar LAT approach, but for oligoprogressive, rather than oligometastatic, disease. Specifically, we are using the term OPD in ALK+ NSCLC to describe the emergence of a limited number of isolated areas of eCNS resistance to a targeted therapy when the majority of disease remains under ongoing control.

Data from rebiopsy series in crizotinib-resistant patients suggest that individual resistant subclones may be selected in a “Darwinian” manner [5, 6]. Consequently, if these subclones are detected prior to dissemination, an early state of progression could exist whereby LAT could delay progression until a new subclone arises. Alternatively, even if the subclone has already microscopically spread, debulking the area(s) of resistance may delay the point at which the predominant resistant disease eventually overwhelms the patient and effectively terminates meaningful benefit of the original targeted therapy. By extending the time of clinically useful systemic disease suppression by the targeted therapy, and thus delaying the time to lethal systemic burden of disease, the patient might derive a survival benefit.

In this study, we have demonstrated that patients who derive clinical benefit from crizotinib and who develop single or multiple episodes of eCNS OPD could be maintained on crizotinib for extended periods of time through the use of LAT. Central to radiotherapeutic LAT is the notion that development of crizotinib resistant clones does not signify resistance

to radiation. With a median of almost 12 months of follow-up in the LAT patients, our findings indicate that radiotherapeutic LAT has excellent LC rates and lesion control is durable in survivors. A dose response was observed in this experience (Figure 2b and c). However, interpretation of these results need to be tempered as they are drawn from multiple local failures in a single patient. More patients and longer follow-ups are needed to further characterize these initial findings. Of note, late or chronic side-effects from LAT may be particularly important to consider because of the prolonged OS of ALK+ lung cancer patients treated with crizotinib [16–18]. Fortunately, no grade 3–5 toxicities were observed in our series.

The median PFS on crizotinib in ALK+ NSCLC has been reported as ranging from approximately 8 to 10 months [4, 7, 19]. Nearly 50% of ALK+ patients initially progress on crizotinib within the CNS and this is likely due to inadequate drug penetration [9, 20]. Consequently, eCNS PFS is probably a better representation of the true time to the development of biological mechanisms of resistance. Consistent with this, in our series, while the median overall PFS was comparable to literature values at 9.1 months, the median eCNS PFS was notably longer at 17 months. We had previously reported in a mixed EGFR mutant and ALK+ population being treated with the relevant targeted therapy, that a single course of LAT for eCNS OPD was associated with 4 months of PFS benefit [9]. Here, looking only within the ALK+ population and with longer follow up, the initial median PFS extension from LAT was 5.5 months, which exceeded the interval between surveillance scans 2–3 fold suggesting that this reflected true benefit from the intervention. Consistent with this, a recent report from Memorial Sloan Kettering, suggested that the use of LAT for OPD (predominantly with surgical approaches) in 18 EGFR mutant patients was associated with a 10 month median PFS extension from PFS1 (95% CI: 2–27 months) [21].

Although there appears to be clear benefit from LAT in individual lesions, determination of the true benefit of LAT to the individual patient requires more investigation. Using multiple courses of LAT to treat OPD, the median duration of exposure to crizotinib was doubled. Remaining on crizotinib for over 12 months was associated with a significant improvement in 2 year OS. These findings support the idea that elimination of limited sites of emerging, resistant disease while remaining on crizotinib in order to maintain suppression of all other sensitive disease could meaningfully extend OS. However, alternative explanations and several caveats about our data must be considered.

Firstly, and most obviously, patients who live longer may have a greater duration of exposure to crizotinib simply because they are alive to take the treatment, without there being any casual relationship present. Secondly, an OPD-type of progression may be a marker for better prognosis/and more indolent disease. Our own findings indicate that patients selected for LAT had a longer median PFS1 compared to the non-LAT eligible cohort (14 vs 7.2 months) supporting this notion. A similar trend towards OPD being associated with a more indolent course was noted in EGFR mutant patients in the Memorial Sloan Kettering study [21]. Finally, given emerging data on the benefits of continuing TKI treatment beyond initial progression for both EGFR TKIs in EGFR mutant NSCLC and for crizotinib in ALK+ NSCLC, we also have to consider the possibility that the benefit may

primarily come from these patients continuing the TKI, rather than from LAT alone or in combination with this approach [22, 23].

Randomized studies at the time of OPD comparing LAT vs no LAT will be required. Defining the most appropriate criteria for employing LAT at the time of OPD will also be needed. In our study we elected to choose a total of 4 OPD lesions as our criteria for considering cases suitable for LAT, but the ideal number to select patients who might benefit from LAT vs those whose disease is too far advanced might be higher or lower. Alternatively, a better metric for distinguishing patients who do or do not benefit from LAT might be a volumetric composite of all active disease that accounts for total lesion volume [24]. In our series, the time between PFS1 to PFS2 in the patients receiving LAT suggested a trend that patients with >2 lesions had a shorter PFS2 compared to those with 2 lesions. However, if subsequent progression events are also treatable with LAT, the duration of each period of progression free survival alone may not be the most informative endpoint to consider. Instead, overall survival, quality of life and health economic endpoints may be needed to address the true benefit from LAT in any future studies.

CONCLUSION/RECOMMENDATIONS

The use of one or more courses of LAT for the treatment of OPD may be a promising method to extend the duration of clinical benefit from crizotinib in ALK+ NSCLC. LAT for OPD was feasible, associated with excellent local control rates and with minimal toxicity. Increased duration of treatment with crizotinib was associated with improved OS. This experience suggests that patients with 1–4 sites of eCNS OPD, appropriate for LAT, could obtain excellent local control of individual lesions. Lesions treated with a higher total dose or SFED were associated with higher rates of local control. Further work is necessary to define the maximum number of lesions and courses of LAT that can reasonably be delivered and the true clinical benefit of these interventions in terms of PFS and OS benefit in patients.

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Summary

The use of radiation therapy as local ablative therapy (LAT) provides excellent and durable local control rates with acceptable low toxicity when managing extra-CNS (eCNS) oligoprogressive disease in advanced ALK+ non-small cell lung cancer patients receiving crizotinib. This paradigm of applying LAT for discrete foci of crizotinib-resistant clonogens allowed for prolonged systemic disease stability and extended utilization of crizotinib, which was associated with an improvement in overall survival.

Figure 1.
Schema illustrating eCNS or CNS progression while on crizotinib and those with eCNS OPD considered appropriate for LAT.

Figure 2A.

Figure 2B.

Figure 2C. **Figure 2.**

KM actuarial local control. (A) Overall local control for individual eCNS lesions treated with radiotherapy alone ($n = 29$). (B) LCRs based on total dose for lesions receiving <40 Gy (red) and lesions receiving ≥ 40 Gy (blue). (C) LCR based on SFED for lesions receiving >25 Gy (blue) and lesions receiving ≤ 25 Gy (red).

Figure 3.

Evaluating KM median PFS1 and overall time on crizotinib in patients who received eCNS LAT. Time is measured from start of crizotinib to time of first progression or maximum time while on crizotinib.

Figure 4.

PET/CT scans evaluating pre-treatment burden of disease and OPD while on crizotinib. (A) Baseline scan prior to initiating crizotinib therapy demonstrates extensive FDG-avid abdominal disease. (B) After 2 cycles of crizotinib therapy, PET/CT scan shows resolution of FDG-avid disease. (C) After 8 months on crizotinib, development of OPD (right adrenal nodule, red circle) subsequently treated with SBRT. (D) After 12 months on crizotinib, a second site of OPD in a retroperitoneal lymph node (LN) (red circle), treated with a 2nd course of SBRT. (E) After 14 months on crizotinib, a 3rd site of OPD in a para-aortic LN (red circle) and treated with a 3rd course of SBRT. (F) After 17 months on crizotinib, a 4th site of OPD seen in a mesenteric LN closely approximated to her small bowel. Because of the location and concern for exceeding small bowel tolerance with additional radiotherapy, no additional LAT was given and patient was discontinued from crizotinib clinical trial and switched to cytotoxic chemotherapy. Of note, after 17 months of therapy, the vast majority of the original sites of FDG-avid disease noted in panel A were still under excellent control with the crizotinib.

Figure 5A **Figure 5B** **Figure 5.**

KM OS of all patients (A); and subdivided by length of time on crizotinib (≤12 versus >12 months) and its affect on OS (B). Time is measured from start of crizotinib until last known follow-up or time of death.

Table 1

Patient Characteristics

	Total	LAT*	Non-LAT*
Number	38	14	13
Age (median, yrs)	55	62	53
Range	23 – 80	29 – 72	29 – 69
Sex			
Male	20 (53%)	7 (50%)	8 (62%)
Female	18 (47%)	7 (50%)	5 (38%)
Race			
Caucasian	33 (87%)	14 (100%)	9 (69%)
Hispanic	3 (8%)	0 (0%)	3 (23%)
Other	2 (5%)	0 (0%)	1 (8%)
Smoking Status			
Never	26 (68%)	9 (67%)	6 (46%)
Former	8 (21%)	5 (25%)	5 (63%)
Current	4 (11%)	0 (0%)	0 (0%)
No. Lines of Therapy Prior to Initiating Crizotinib	3 (1–6)	2.5 (1–4)	3 (2–5)

* These patient numbers only include those with eCNS progression and do not include patients who had not yet progressed (n = 5) or those who presented with CNS only progression (n = 6)