ORIGINAL ARTICLE

Consolidative Local Ablative Therapy Improves the Survival of Patients With Synchronous Oligometastatic NSCLC Harboring EGFR Activating Mutation Treated With First-Line EGFR-TKIs

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ABSTRACT

Introduction: The aim of the current study was to investigate whether consolidative local ablative therapy (LAT) can improve the survival of patients with stage IV *EGFR*-mutant NSCLC who have oligometastatic disease treated with first-line EGFR–tyrosine kinase inhibitor (TKI) therapy.

Methods: Patients with stage IV *EGFR*-mutant NSCLC and no more than five metastases within 2 months of diagnosis were identified. All patients were treated with first-line EGFR-TKIs. Consolidative LAT included radiotherapy, surgery, or both. Overall survival (OS) and progression-free survival (PFS) were estimated by Kaplan-Meier curves.

Results: From October 2010 to May 2016, 145 patients were enrolled, including 51 (35.2%) who received consolidative LAT to all oligometastatic sites (all-LAT group), 55 (37.9%) who received consolidative LAT to either primary tumor or oligometastatic sites (part-LAT group), and 39 (26.9%) who did not receive any consolidative LAT (non-LAT group). The median PFS in all-LAT, part-LAT, and non-LAT groups were 20.6, 15.6, and 13.9 months, respectively ($p < 0.001$). The median OS in all-LAT, part-LAT, and non-LAT groups were 40.9, 34.1, and 30.8 months, respectively ($p < 0.001$). The difference was statistically significant between the all-LAT group and part-LAT or non-LAT group but was not between the part-LAT and non-LAT group. The median OS was significantly improved with consolidative LAT for primary tumor (40.5 versus 31.5 months, $p < 0.001$), brain metastases (38.2 versus 29.2 months, $p = 0.002$), and adrenal metastases (37.1 versus 29.2 months, $p = 0.032$). Adverse events (grade ≥ 3) due to radiotherapy included pneumonitis (7.7%) and esophagitis (16.9%).

Conclusions: The current study showed that consolidative LAT to all metastatic sites was a feasible option for patients with *EGFR*-mutant oligometastatic NSCLC during first-line EGFR-TKI treatment, with significantly improved PFS and OS compared with consolidative LAT to partial sites or observation alone.

Keywords: Oligometastases; Consolidation; Local ablative therapy; EGFR–tyrosine kinase inhibitor; NSCLC

Introduction

Landmark clinical trials have shown that advanced NSCLC patients with activating *EGFR* mutations have higher response rates and better progression-free survival (PFS) when treated with EGFR tyrosine kinase inhibitors (TKIs) compared with classical platinum-based chemotherapy.[1-4] However, progression inevitably

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develops in most cases after 1 to 2 years of EGFR-TKI treatment.[5] When acquired resistance occurs, approximately one-fourth of patients experience local progression.[6] For patients with oligoprogressive disease, local ablative therapy (LAT) plus continuation of EGFR-TKIs could result in more than 6 months of additional clinical benefits.[7] Therefore, LAT is a reasonable option for patients with oligoprogressive resistance to EGFR-TKIs.

Previous studies have revealed that stage IV disease with oligometastases can represent an indolent phenotype that could benefit from LAT for consolidation.[8] In a multicenter randomized controlled phase 2 study, local consolidation therapy with radiotherapy or surgery especially can significantly prolong PFS for patients with oligometastatic NSCLC ($\leq$3 sites) who have disease control after initially systemic therapy.[9] However, data regarding the optimal consolidative LAT for patients with stage IV *EGFR*-mutant NSCLC who have oligometastatic disease during first-line EGFR-TKI therapy are sparse.[9-12] We hypothesized that consolidative LAT for patients with oligometastases could also offer survival benefits during first-line EGFR-TKI treatment. To address this issue, we investigated the survival outcomes of patients with stage IV *EGFR*-mutant NSCLC treated with first-line EGFR-TKI therapy with or without consolidative LAT.

Materials and Methods

Patients

A retrospective study was conducted in patients with stage IV *EGFR*-mutant NSCLC who had oligometastatic disease within 2 months of diagnosis from October 2010 to May 2016 at Shanghai Pulmonary Hospital. Patients who met the following criteria were enrolled: pathologically confirmed NSCLC with *EGFR* sensitizing mutation (exon 19 deletion or exon 21 L858R mutation), stage IV disease according to the 7th edition of the American Joint Committee on Cancer staging system, with synchronous oligometastatic disease (five or fewer metastases within 2 months of diagnosis in one to multiples organs, excluding primary tumor), 18 years of age or older, with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of 2 or less, and did not progress after initial first-line EGFR-TKI treatment. Tumor stage was assessed by systemic imaging (either contrast-enhanced computed tomography [CT] of the chest, abdomen, bone scan, or positron-emission tomography [PET]/CT) and brain imaging (either contrast-enhanced CT or magnetic resonance imaging).

Baseline characteristics were obtained from electronic records, including age at diagnosis, sex, smoking status, ECOG PS, histology, TNM stage, *EGFR* mutational status, oligometastatic sites, number of oligometastatic disease, and subsequent treatment. Treatment response was evaluated 6 to 8 weeks after the initiation of therapy according to Response Evaluation Criteria in Solid Tumors version 1.1. EGFR-TKIs used in this study included gefitinib (250 mg, once a day), erlotinib (150 mg, once a day), and icotinib (125 mg, three times a day).

EGFR mutations were tested by an amplification refractory mutation system (Amoy Diagnostics Co., Ltd., Xiamen, China) as described in our previous studies.[13-15] All mutational analyses were performed at the Thoracic Cancer Institute, Tongji University School of Medicine, Shanghai, China. This study was approved by the ethics committee of Shanghai Pulmonary Hospital and written informed consent to use the clinical data for research was obtained from each participant before the medical intervention started.

The Procedures of LAT

The types of consolidative LAT included surgery, radiotherapy, or both and were determined in consultation with multidisciplinary teams (including medical oncologists, radiation oncologists, radiologists, and surgeons), according to patients' age, cardiopulmonary function, tumor location, benefit-risk evaluation, as well as patient preference. The choice of dose-fractionation regimen was made by the treating radiotherapist, with curative intent when possible. Accepted definitive radiotherapy included standard-fractionation radiotherapy (60 Gy in 2-Gy fractions) or aggressive palliation radiotherapy (45 Gy in 3-Gy fractions, a biologically equivalent dose of approximately 60 Gy), stereotactic radiosurgery (SRS) (21 to 27 Gy in single-fraction; 26.5 to 33.0 Gy in 3-fraction; and 30 to 37.5 Gy in 5-fraction), and whole brain radiotherapy (WBRT) (30 Gy in 3-Gy fractions). SRS was usually used for tumors up to 5 cm in size and there was no limitation of tumor size for patients who received conventional radiation. For liver metastases, radiofrequency ablation was accepted.

According to consolidative LAT to residual sites, patients were divided into 3 groups: the all-LAT group (consolidative LAT to all residual disease, including primary tumor, lymph nodes, and metastatic sites as appropriate), the part-LAT group (consolidative LAT to either primary tumor or oligometastatic sites), and the non-LAT group (patients who did not receive any LAT).

Statistical Analysis

Descriptive statistics were used to summarize patient characteristics by treatment group. The categorical variables were compared using the chi-square test or Fisher's exact test. PFS was defined as the time from treatment commencement of EGFR-TKI to confirmed disease progression or death of any cause. Overall survival (OS) was defined as the period from the date of the time from treatment commencement of EGFR-TKI to the date of death. Kaplan-Meier curve and log-rank test were